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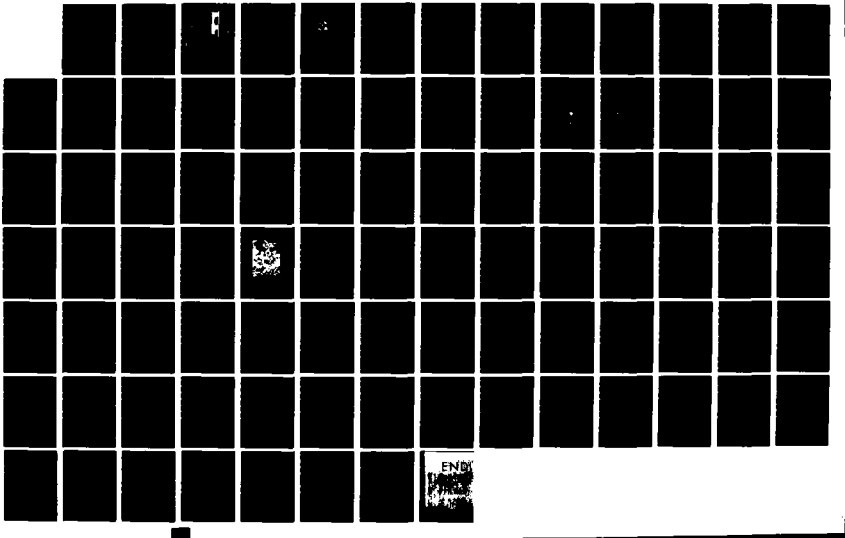

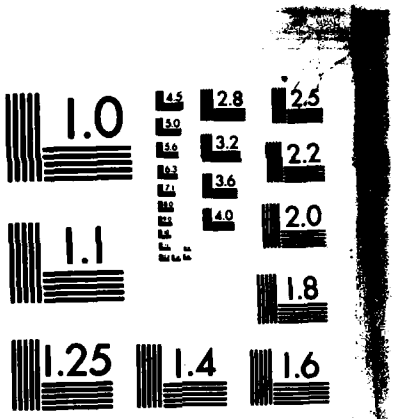

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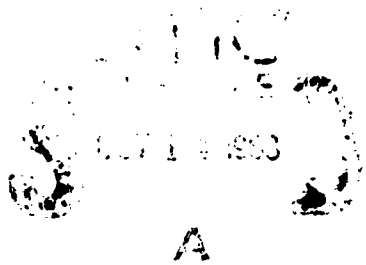
NUTRITIONAL SUPPORT SYMPOSIUM
PRESENT CONCEPTS IN INTERNAL MEDICINE

MAJ David S. Keisler, Jr., MD, MC and Nina Z. Sanders, B.A.

Letterman Army Medical Center
Presidio of San Francisco, CA 94129

Summer 1983

Nutritional Support Symposium



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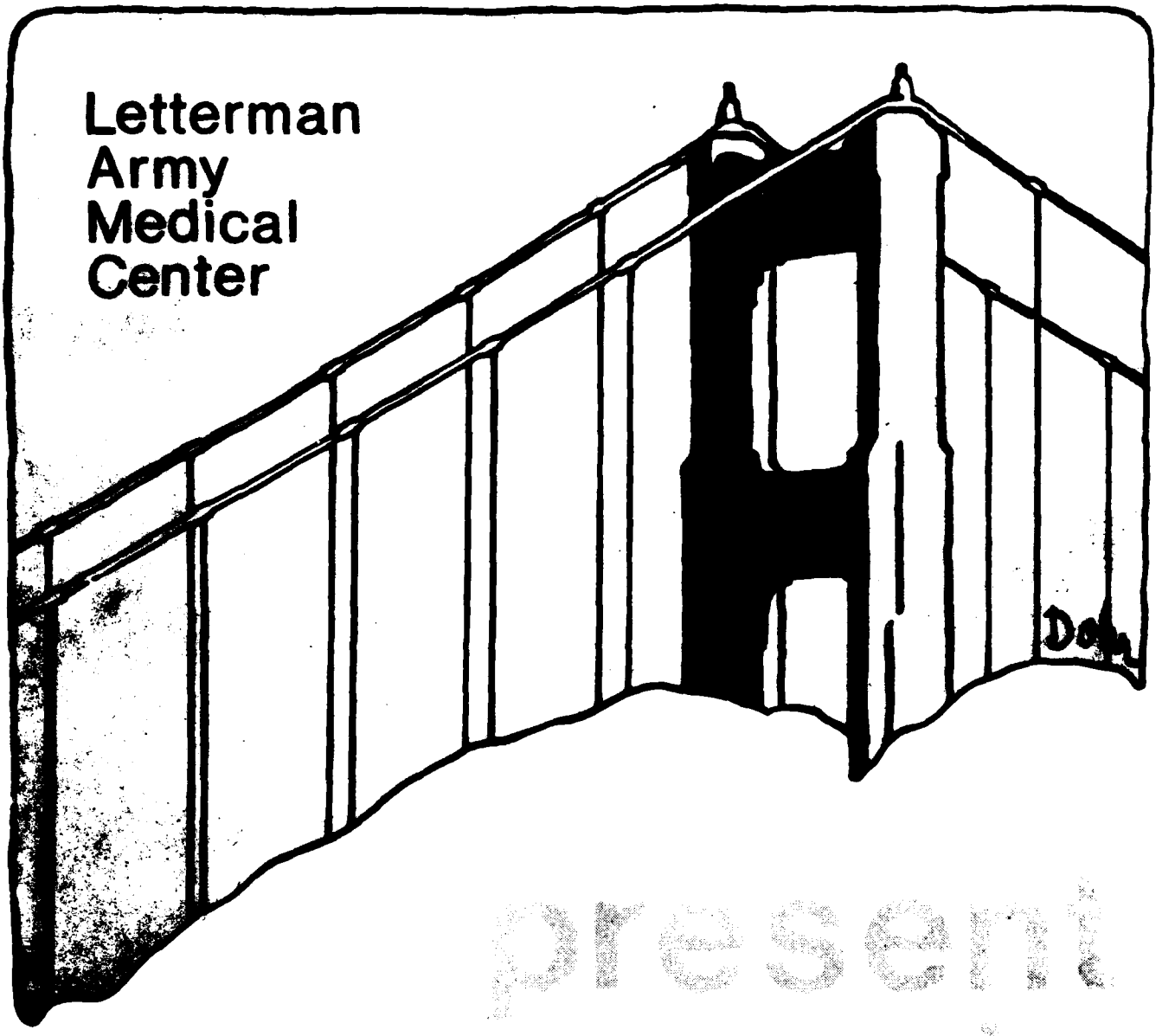

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in Internal Medicine

NUTRITIONAL SUPPORT SYMPOSIUM, VOL. 14, NO. 1, SUMMER 1983

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Total parenteral nutrition; nutritional assessment; nutrient and hormonal adaptations; peripheral parenteral nutrition; enteral alimentation.

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

This symposium consists of eight articles, three appendices, seven tables, and four figures. It includes articles on total parenteral nutrition; nutritional assessment; nutrient and hormonal adaptations to starvation; infectious consequences of malnutrition; minerals, vitamins and trace elements in parenteral nutrition; enteral alimentation; and writing total parenteral nutrition orders.

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PRESENT CONCEPTS
IN INTERNAL MEDICINE

David S. Keisler, Jr., MD
Major, Medical Corps, *Editor*

Nina Z. Sanders, BA
Technical Publications Editor

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Herman L. Price, MD
Colonel, Medical Corps
Chief, Department of Medicine

Frank F. Ledford, Jr., MD
Brigadier General, Medical Corps
Commander

LETTERMAN ARMY MEDICAL CENTER
Presidio of San Francisco, California 94129

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PRESENT CONCEPTS IN INTERNAL MEDICINE

Nutritional Support Symposium

CONTENTS

Department of Medicine
LETTERMAN ARMY MEDICAL CENTER
PRESIDIO OF SAN FRANCISCO, CALIFORNIA 94129

DEDICATION

This issue of PRESENT CONCEPTS IN INTERNAL MEDICINE is dedicated to Betty L. Young. Where others would be content to swim against the current, Mrs. Young has succeeded in reversing the flow. We at Letterman Army Medical Center share enthusiastic admiration for this unique patient who has always had faith in us and in Army Medicine.

FOREWARD

Effective problem-solving in clinical medicine and surgery requires that the physician develop a broad base of knowledge. In an attempt to expedite therapy, the field of nutrition is frequently overlooked, yet malnutrition remains one of the major causes of death among critically ill hospitalized patients. This issue of PRESENT CONCEPTS IN INTERNAL MEDICINE has been prepared to assist you in the management of many of the nutritional problems you may encounter in your medical pratice.

DAVID S. KEISLER, JR., MD
Major, Medical Corps
Gastroenterology Service
Guest Editor

LIST OF ABBREVIATIONS

AMA - American Medical Association
AMP - adenosine monophosphate
ATP - adenosine triphosphate
BEE - basal energy expenditure
CAT - carnitine acyl transferase
CBC - complete blood count
CHF - congestive heart failure
CHI - creatinine-height index
CNS - central nervous system
DNA - deoxyribonucleic acid
FAD - flavin adenine dinucleotide
GI - gastrointestinal
IBW - ideal body weight
IM - intramuscularly
IU - international unit
IV - intravenous
Kcal - kilocalorie
LAMC - Letterman Army Medical Center
LIVN - Letterman intravenous nutrition solution
NAD - nicotinamide-adenine dinucleotide
PPN - peripheral parenteral nutrition
PT - prothrombin time
PTT - partial thromboplastin time
RDA - recommended daily allowance
SGOT - serum glutamic-oxaloacetic transaminase
SGPT - serum glutamic-pyruvic transaminase
SMAC-20 - sequential multiple analyzer computer
SKSD - streptokinase-streptodornase
TIBC - total iron-binding capacity
TPN - total parenteral nutrition
UUN - urinary urea nitrogen
VLDL - very low-density lipoprotein

TOTAL PARENTERAL NUTRITION AT LETTERMAN ARMY MEDICAL CENTER

MAJ David S. Keisler, Jr., MD, MC

Malnutrition and infection are major causes of death in critically ill hospitalized patients. /1/ These two complications can be avoided if physicians assess their patients properly, and if sound nutritional therapy is available. Kawashiokor and marasmus are the classic examples of malnutrition, but less severe forms of protein-calorie malnutrition are not difficult to find; usually, there are several cases on every medical and surgical ward. /2/

Decreased oral intake, increased enteral losses, and increased nutritional requirements due to hypermetabolism resulting from sepsis or trauma are common causes of protein-calorie malnutrition. /3/ Patients who are unable or unwilling to eat, and patients with specific organ dysfunction and special nutritional requirements (cardiac, renal, or liver failure, short-gut syndrome) require nutritional support. /4/

Patients who cannot ingest enough calories to satisfy nutritional requirements may need to be supported with total parenteral nutrition (TPN) through a central line.

Indications for parenteral nutrition are outlined in Grant's text /4/ as follows:

1. Protein-calorie malnutrition
    a. Anorexia nervosa
    b. Chronic vomiting
    c. Malabsorption syndrome
    d. Prolonged ileus or gastrointestinal malabsorption
2. Short bowel syndrome
3. Acute pancreatitis and pancreatic fistulas

4. Enterocutaneous fistulas
5. Inflammatory bowel disease
6. Malignant disease
7. Renal failure
8. Hepatic failure
9. Hypercatabolic states
10. Burns
11. Trauma

Nutritional assessment is determined by using the methods outlined in Dr. Goldner's article, pp. 13-21. This process does not need to be extraordinarily complicated. Serum albumin, serum transferrin, degree of weight loss, and total lymphocyte count are easily obtainable at Letterman Army Medical Center (LAMC) and are good parameters to follow.

A calorie is the unit used to express the amount of heat required to raise the temperature of 1 gm of water 1 °C. /5/ This is too small a unit to relate to the body energy requirements and, therefore, the kilocalorie (kcal), which actually represents 1,000 calories, is used.

Basal energy expenditure (BEE) is the predicted calorie expenditure of a resting, fasting, unstressed patient. /6/ For the average 70-kg man, this is approximately 1,800 kcal per day. The BEE is determined by using the Harris-Benedict equation, as follows: /6/

Men:	$66 + 13.7W + 5H - 6.8A$ (kcal/day)
Women:	$665 + 9.6W + 1.7H - 4.7A$ (kcal/day)
Infants:	$22.10 + 31.05W + 1.16H$

(H = height in cm; w = weight in kg; A = age in years)

Wilmore uses body surface area and standard metabolic rates to determine the calorie requirement. This method requires the use of normograms described in his text. /1/

Extra calories, required by patients with stress and fever, can be outlined as follows:

ADD:

0.2 BEE for daily activity

0.2 BEE for fever to 39 °C

0.3 BEE for fever 39.2 °C to 40.0 °C

0.4 BEE for fever greater than 40.0 °C

0.2 BEE for postoperative days 0-7

0.2 BEE for sepsis

0.4 to 0.8 BEE for tumor

0.4 to 1.0 BEE for severe burns

Maximum calories = 2 X BEE

Add 500 to 1,000 kcal/day for weight gain of 0.5 to 0.9 kg/wk.

The energy sources used in TPN are supplied by carbohydrates, proteins, and fats. Carbohydrates and protein each supply 4 kcal/gm, and fat supplies 9 kcal/gm.

Crystalline amino acids and protein hydrolysates are both used as protein sources. Protein with a low concentration of essential to non-essential amino acids is said to have a low biologic value. /1/ To convert grams of protein to grams of nitrogen, divide grams of protein by 6.25. To determine the nitrogen output of a patient, measure the 24-hour urinary urea nitrogen (UUN) and add another 20% UUN, plus 2 gm. To determine the nitrogen balance, subtract the output as determined above from the intake in the TPN solution. The nitrogen intake is adjusted to achieve a positive nitrogen balance of 2.0 to 5.0 gm/day. The oral

protein requirement for healthy adults is recommended at 0.3 gm/kg/day. /4/ The Letterman intravenous nutrition solution (LIVN) contains a 10% Aminosyn™ solution that supplies 4 gm/nitrogen/L. Three liters of solution per day would, therefore, deliver 16 gm of nitrogen. For the special patient with fluid overload, hepatic, or renal failure, whose protein may need to be restricted, it is advisable to obtain consultation from the gastrointestinal or renal service. Basically, nitrogen requirements range from 0.08 to 0.16 gm/kg/day.

Fat provides more energy per gram than do the other two fuels. Fat is supplied as a 10% or 20% emulsion to patients on TPN to provide calories and to prevent essential fatty acid deficiency. Side effects are associated with administration of intravenous (IV) fat solutions. Lipid emulsions may be contraindicated in patients with severe pulmonary disease, diabetes mellitus, liver disease, coagulopathy and thrombocytopenia, and abnormalities in lipid metabolism. /1/

Much controversy centers around the optimal amount of fat that should be given to patients on TPN. Essential fatty acid deficiency can be avoided by infusing 500 cc of a 10% solution every other day. Serum triglyceride levels should be determined before therapy and monitored closely during hospitalization. Fat emulsions should be infused slowly (500 cc/8 hr) without a filter and through a peripheral vein or via a Y-connector system.

Carbohydrates, the third essential fuel, are supplied in TPN solutions as dextrose. LIVN contains 30% dextrose; one liter provides about 1,000 non-protein calories. Healthy adults should be able to metabolize 0.3-0.4 gm/kg/hr of IV glucose. /4/ Hypertonic glucose solution can be safely administered only through a catheter in a central vein. High carbohydrate intake can cause hyperglycemia and hyperomolarity, resulting in hypovolemia, dehydration, and coma. Infusions should, therefore, begin slowly and run continuously. We usually begin at 40 cc/hr on the first day, advancing to 80 cc/hr and 120 cc/hr on the second and third days, as tolerated. Glycosuria and hyperglycemia (blood glucose greater than 180-200 mg%) can be managed with insulin or by decreasing the rate of infusion. It is dangerous to administer insulin without knowing the value of the serum postassium.

It is important to maintain normal serum glucose levels in order to avoid the complications of hyperglycemia. Rapid changes in blood sugar can be avoided by adding insulin directly to the TPN solution bottle. We try to maintain the serum glucose level below 150 mg%. If glycosuria occurs, Grant /4/ recommends giving insulin intramuscularly to avoid erratic absorption from the subcutaneous route. Recommended dosage is 5-8 units of regular insulin for 3+ glycosuria and 10-12 units for 4+ glycosuria, every 4-6 hours, as needed.

Estimates for fluid and electrolyte requirements are made in the standard manner and are not discussed here.

Vitamins and trace elements are added to each bottle of standard LIVN solution. Vitamin K should be given in a dosage of 10 mg/week, intramuscularly. (For contents of standard TPN solution used at LAMC, see APPENDIX I.)

While TPN may be life-saving, complications can arise; do not start a patient on LIVN unless you are prepared with those potential problems.

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NUTRITIONAL ASSESSMENT
Why is Nutritional Assessment Important?

LTC Fred H. Goldner, MD, MC

Although signs of extreme cases of malnutrition, e.g., cachexia or edema, may be obvious, lesser degrees often go undetected. Indeed, from 30-50% of patients currently hospitalized are malnourished and, in most cases, the malnutrition is unrecognized. /1/ Because numerous diagnostic tests and therapeutic regimens (chemotherapy, radiotherapy) interfere with nutrition, the nutritional status of many hospitalized patients deteriorates rather than improves.

Detection and correction of malnutrition are more than an academic exercise. Numerous studies show that malnourished patients are at greater risk from surgery, have longer wound healing, and have greater incidence of infection and mortality than well-nourished patients. /2/ Cancer patients must have an adequate nutritional status in order to tolerate and respond to chemotherapy and radiotherapy regimens. Thus, it is essential that physicians make an effort to determine the nutritional status of each patient.

TERMINOLOGY

1. Marasmus. Although the diet may contain an acceptable protein-to-calorie ratio, the total dietary intake is inadequate, leading to loss from all body compartments, including fat deposits and muscle mass. Typically, patients with marasmus are easy to identify by their cachectic appearance.

2. Kwashiorkor. Associated with a diet of ample calories primarily of carbohydrate origin and little or no protein, this disease is manifested as a decrease in serum proteins and edema. Findings may be obscured, however, by coincidental obesity generated by ample caloric intake.

3. Mixed Malnutrition. The most common form of malnutrition, with aspects of both marasmus and kwashiorkor. Care must be exercised not to overlook one form because of the severity of the other.

STANDARD TECHNIQUES OF NUTRITIONAL ASSESSMENT

While more quantifiable methods are discussed elsewhere /3,4/, the cornerstone of nutritional assessment remains a thorough history and physical examination.

1. Clinical and Dietary History. Certainly, an effort should be made to estimate the caloric intake of all patients. Of importance are questions concerning fad diets, general appetite, dentures, living alone, food budget, recent weight change, nausea, vomiting, diarrhea, and level of alcohol consumption. Specific deficiencies in iron and calcium should be suspected in patients who have had gastric surgery.

2. Physical Examination. Unfortunately, signs of nutritional deficiencies are apparent only in severe cases. Nevertheless, evidence of muscle wasting, ascites, hepatic enlargement, and fat depletion is of great importance. The physician should look for specific signs of vitamin deficiencies, including deficiencies of vitamin B_5, niacin, which may result in pellagra, and vitamin B_1, thiamine, which may cause beriberi or Wernicke's encephalopathy. Trace metal deficiencies such as zinc deficiency, leading to diarrhea, dermatitis, hair loss and loss of taste and smell, are being detected with increasing frequency.

BODY COMPOSITION ANALYSIS

When assessing the patient's nutritional status, one should consider the various body fuel sources and compartments separately, since they differ in function and metabolic importance. These compartments include: (1) fat; (2) somatic protein (muscle); and (3) visceral protein (serum and organ protein). The proportion and metabolic value of each are shown in Fig. 1. It must be stressed that the object of

nutritional support is to defend and support protein metabolism. Unlike fats and carbohydrates, protein cannot be stored. Every protein in the body, whether in connective tissue, lymphocytes, or enzymes, has a function. If protein is eroded to provide fuel for metabolic processes, the body suffers in a functional, not merely cosmetic, manner. This is not to imply that proteins are static; rather, they are constantly being remodeled. Indeed, 40% of the body's resting energy expenditure is directed toward protein turnover, yet the total body protein pool is maintained. While fat provides the bulk of storage calories, fatty acids, unlike amino acids, cannot be utilized for glucogenesis. Thus, there is an obligatory catabolism of protein if serum glucose is to be defended. In prolonged fasting, however, the body is able to convert to burning fatty acids directly. Obviously, then, evaluation of the protein compartments is most crucial.

ASSESSMENT TOOLS

1. Fat. Approximately 50% of the total body fat is deposited in the subcutaneous layers, making it accessible to measurement. The most commonly used clinical tool is the anthropometric measurement of skin-fold thickness, usually in the triceps or subscapular area (Fig. 2). /5,6/ For such measurements to be reliable, standard sites and techniques are necessary. To determine triceps skin-fold thickness, measure the distance between the acromial and olecranon processes, mark the midpoint on the posterior aspect of the arm, and apply a large skin fold caliper to exert a constant force. The distance between the prong tips is measured in millimeters. Repeat measurements must be made in the same manner. Measure subscapular skin-fold thickness 1 cm below the tip of the right scapula.

Comments: While fat stores are important, they change slowly and may remain relatively normal in kwashiorkor-like states in the face of decreased body protein. Unless premorbid anthropometric measurements are available for a particular patient, the measurement must be compared to values from standard tables. These values represent averages from large groups of "normal" people and may not reflect the actual premorbid situation for a particular patient. Measurements may

also be misleading if edema or subcutaneous emphysema is present. In addition, measurements made by different examiners on different days may vary up to 22%.

2. Somatic Protein. Muscle mass is as difficult as fat to measure. Methods to measurement include:

a. Ideal body weight (IBW), or current weight as a percent of IBW. The IBW is derived from standard tables, e.g., Metropolitan Life Insurance Company, which show averages of large populations and require estimates of frame size (Small, Medium, Large). (No guidelines are provided for estimating frame size.) Weight determination measures fat loss, as well as protein loss.

b. Recent weight change (usual weight minus current weight over usual weight, times 100). This method is more reliable than methods that rely on IBW tables. Weight loss greater than 10% of usual weight is regarded as clinically significant.

c. Mid-upper arm circumference. This measurement, in centimeters, is taken in the same place as the triceps skin-fold measurement, and comparisons are made, by sex, using a percentile table. Despite the apparent simplicity of this measurement, its reproducibility, even by the same observer, is inconsistent; hence, small changes are not readily detectable. /7/

d. Creatinine-height index (CHI). This measurement is based on the principle that creatin (metabolized to creatinine) is produced by muscle in constant proportion to its mass. The 24-hour creatinine may be used to measure muscle mass relative to the population norm. The CHI, therefore, is the (Cr) measured over the (Cr) expected. The (Cr) expected is calculated as follows: Determine height and look up the ideal medium frame weight for that height in the Metropolitan Life Insurance Company tables. Calculate the (Cr) expected for males as 23 mg/kg/d and for females as 18 mg/kg/d. Again, these measurements are subject to all the shortcomings of table analysis as well as the known difficulties of collecting accurate 24-hour urine outputs.

3. Visceral Protein. Two general categories are considered: Serum transport protein and immunologic functional measurement.

a. Serum transport proteins. The ideal protein should have a short half-life in order to respond quickly to catabolic changes and should be measurable in the average hospital laboratory. The two proteins most commonly used are:

(1) Albumin. With a large total body pool of 4-5 mg/kg and a relatively long half-life of 20 days, albumin falls short of being the ideal protein to measure. Also, decreased production from liver disease and increased loss (proteinuria) may confuse interpretation for nutritional purposes. As a general rule, the following values are guidelines to degrees of nutritional depletion:

Serum (gm%)	Depletion
2.8 - 3.5	mild
2.1 - 2.7	moderate
< 2.1	severe

(2) Transferrin. The shorter half-life of 8-10 days makes this protein more valuable than albumin. Transferrin may be calculated from the total iron-binding capacity (TIBC): Transferrin equals 0.8 TIBC minus 43. Normal transferrin is 250-300 mg%. One drawback to transferrin is that it also relates to changes in iron stores and does not reflect solely nutritional status. Other proteins, such as thyroid-binding pre-albumin and retinol-binding protein are more suitable because of a short half-life but, unfortunately, are available in few laboratories.

b. Immunologic Function Measurement. Immunocytes are extremely sensitive to loss of proper nutritional mileau. The measurement of immunologic dynamics is important because it is truly a functional test and not merely a means of measuring concentration. Total lymphocyte count and determination of cell-mediated immunity are the most valuable tests.

(1) Total lymphocyte count. This test can be obtained from any complete blood cell count. The following ranges are associated with degrees of malnutrition:

Ranges (mm)	Degree of Malnutrition
1,200-2,000	mild
800-1,200	moderate
< 800	severe

(2) Cell-mediated immunity. Skin testing using tuberculin, mumps, Candida albicans, tricophytin, and SKSD. Unfortunately, there is no universally accepted relationship of degrees of skin test reactivity to malnutrition, except that total non-reactivity to all antigens (anergy) may reflect severe malnutrition. Overwhelming infection, e.g., tuberculosis, may also cause anergy. Although reactivity may return if rechallenged after nutritional repletion, this may take at least 2 weeks. /8/

RECOMMENDATIONS

In view of the problems and pitfalls associated with each method of measuring malnutrition, the following recommendations are made:

1. Obtain a complete history and physical examination of the patient.

2. Determine the patient's accurate weight and weight changes, using all available resources (e.g., prior hospital records, family).

3. Obtain a CBC and SMAC-20 with attention to albumin and calculate transferrin.

4. Obtain total lymphocyte count.

5. Perform delayed cutaneous hypersensitivity testing.

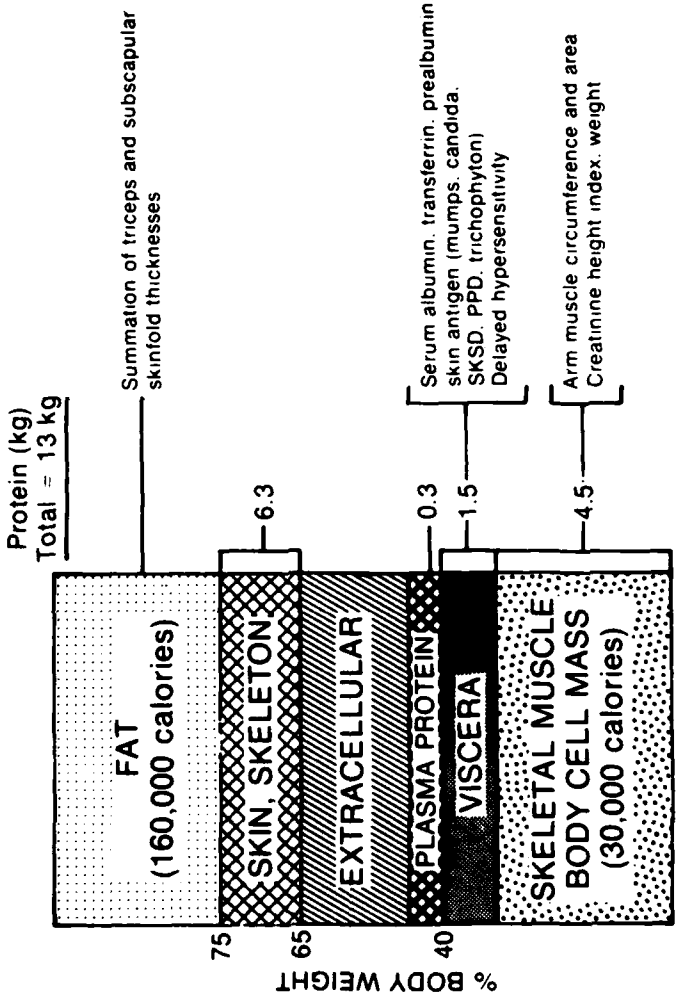

Figure 1. Current techniques for the assessment of nutritional status with corresponding components of body composition. (Modified from Blackburn, G. L., and Bothe, A., Jr.: Assessment of malnutrition in cancer patients. Cancer Bulletin, *30*:90–93, 1978.)
(Reprinted with permission from the authors and the publisher.)

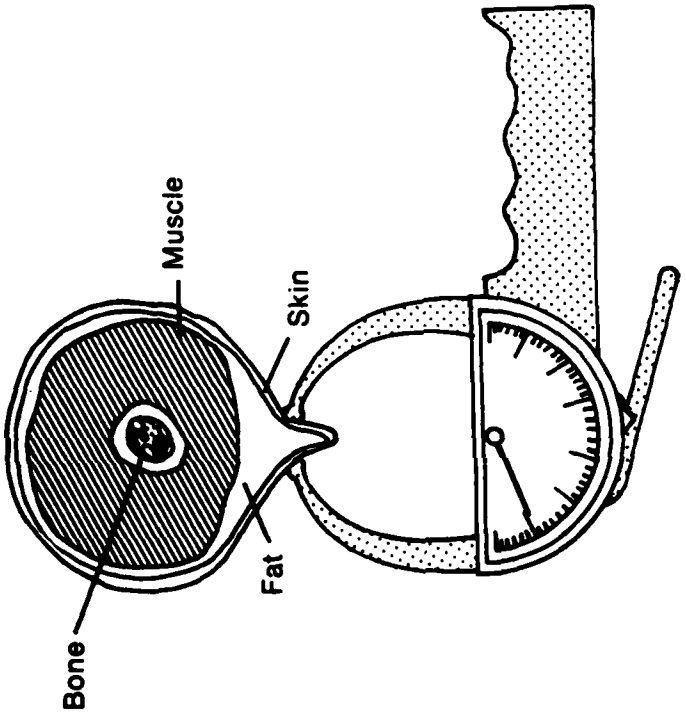

Figure 2. This cross-sectional diagram shows the technique for measuring a skinfold, a double layer of subcutaneous fat and skin. In this case, the triceps skinfold is being measured with the Lange caliper. (*From* Grant, A.: Nutritional Assessment Guidelines. Berkeley, California, Cutter Laboratories, 1979, with permission.)

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NUTRITIONAL PEARLS

Candida albicans is the most common fungal infection in patients receiving total parenteral nutrition solution.

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If a patient requires 2,000 kcal at rest, he will need 2,800 kcal if his temperature rises to 40 °C (104 °F).

"Compassion is the physician's mentor" (Paracelsus).

NUTRIENT AND HORMONAL ADAPTATIONS TO STARVATION

MAJ Robert E. Jones, MD, MC*

The coexistence of stress and semi-starvation in both medical and surgical patients is not uncommon. The purpose of this communication is to provide an overview of the nutrient and hormonal interactions that occur during nutritional deprivation.

The maintenance of vital processes involves overcoming the individual's natural trend toward universal disorder (entropy) by continually replenishing the organism with energy to sustain or increase its degree of order. According to the second law of thermodynamics, this cannot be accomplished without a concomitant increase in randomness elsewhere in the system. Indeed, Banks has established that a man weighing 70 kg must disorder the yearly equivalent of 24 sheep to maintain the appropriate degree of order needed for survival. /1/ It follows, as an unfortunate consequence, that a fasting human can only devour himself, an obviously futile and self-destructive endeavor.

By providing mechanisms for nutrient storage, nature has allowed for short-term adaptation to starvation. Fuels such as carbohydrates, lipids, and amino acids are accumulated in the form of hepatic and sarcoplasmic glycogen, adipocyte, and intracellular triglyceride and protein, respectively. With the exception of protein, which already serves important functions as enzymes or in structural roles, the remaining fuels are principally designed as nutrient depots.

The amount of adipocyte triglyceride varies considerably among individuals; the average man stores about 15 kg of fat, potentially capable of yielding up to 141,000 calories. /2/ In contrast, total glycogen stores in the body

*Endocrinology Service, Department of Medicine
Madigan Army Medical Center, Tacoma, Washington

weigh 225 mg and can contribute only 900 calories in time of caloric need. While it is known that glycogen can be depleted after a few short hours of fasting, the extent to which lipids can support a fasting subject is more obtuse. Conceivably, man can survive on endogenous triglyceride alone for many months /3/; however, this point is moot because of the concurrent depletion of other essential nutrients such as minerals, vitamins, and other substances.

Amino acids (protein) can also donate valuable precursors, hence calories, but proteins also define the organism by providing structural integrity and the catalytic means to derive useful energy from fuel. Rapid auto-cannibalism of protein would prematurely terminate the instrument of adaption to starvation, and efforts are made to conserve this protein reserve.

In summary, when compared with the other depot fuels, lipids play the most prominent role in providing the major source of potential energy and can act to conserve both protein and glycogen for future use.

HORMONAL ADAPTION TO FASTING

During a fast, anabolic pathways are inhibited, and catabolic or amphibolic sequences supervene. This shift in molecular homeostasis is accomplished by hormonal mechanisms and, in part, by the direct effect of substrates on the catalytic rates of selected enzymes.

Insulin plays a pivotal role in this adaptive scheme. As food intake diminishes, circulating insulin levels fall from post-absorptive peaks around 140 μU/ml to less than 20 μU/ml in the fasting state. /4/ At these lower concentrations of insulin, several important events begin to occur: insulin-mediated glucose uptake by peripheral tissues decreases, the activity of adipocyte hormone-sensitive lipase increases, hepatic glucose production via gluconeogenesis is augmented, and *de novo* fatty acid biosynthesis from glucose and the rate of protein synthesis fall. Overall, this reduction in insulin release helps to conserve blood glucose concentrations by promoting glucose production, reducing its

utilization and, at the same time, indirectly providing alternate substrates in the form of free fatty acids for insulin-sensitive tissues.

If caloric deprivation becomes chronic, the levels of glucagon and cortisol may rise. /5/ These counter-regulatory hormones act as additional insurance to guarantee availability of glucose for the central nervous system (CNS) and prime the liver for ketone body generation.

Although not directly involved in the cellular conversion to alternate fuel sources, the down regulation of thyroid hormones during fasting probably plays an important adaptive function by assisting in reduction of basal energy expenditure /6/, and ultimately extends the value of accumulated calories. Specific actions and interactions of each of these hormones are listed in the Table.

Ketogenesis

The ketone bodies (acetoacetate, 3-hydroxybutyrate and acetone) are derived from endogenous triglyceride stores or amino acids and can supplant glucose as a cellular energy source in a variety of tissues, including muscle and the CNS. /7/ A brief period of adaption is required, however, before neurons can efficiently extract and metabolize ketones. /8/

The mechanisms of ketogenesis are rather complex and are under bihormonal regulation through insulin and glucagon. Lipolysis, or release of storage triglyceride as free fatty acids, is facilitated by a relative insulin deficiency and is directly stimulated by glucagon. /9/ Other hormones, namely catecholamines, cortisol, and growth hormone, also enhance the rate of adipocyte triglyceride hydrolysis; cortisol and growth hormones do so by inducing the synthesis of new lipolytic enzymes /10/, hence resetting the cells for a higher potential for fatty acid release, and catecholamines directly augment hormone sensitive lipase through cAMP generation. /10/ These hormonally mediated mechanisms allow both acute and chronic modulation of hepatic delivery of free fatty acids for ketone body production.

In addition to lipolytic properties, glucagon is critical for increasing the ketogenic capacity of the liver independent of insulin or free fatty concentrations. The importance of glucagon is mirrored in studies of ketogenesis during states of glucagon deficiency (total pancreatectomy, somatostatin, *in vitro*) /11-13/, when onset of ketoacidosis is delayed or total capacity of the liver to produce ketones is reduced.

After free fatty acids are taken up by hepatocytes, they are rapidly but reversibly bound to specific cytosolic proteins. /14/ If the binding capacity of these fatty acids binding proteins is exceeded, free fatty acids can interact with a variety of enzymes and can, as a result, modify enzymatic rates.

The next step in ketogenesis is activation of fatty acids by the enzyme fatty acid: CoASH ligase (AMP). /15/ This enzyme, which is actually a family of enzymes, is associated with the outer mitochondrial membrane and converts a free fatty acid to a fatty acyl CoA thio-ester at the expense of ATP hydrolysis to AMP. After activation, these important acyl CoA derivatives must be modified to allow the fatty acid moiety to traverse the inner mitochondrial membrane and enter the matrix region of the mitochondrion where ketones are synthesized. This is accomplished by a group of enzymes collectively known as carnitine acyl transferases (CAT). /16/

CAT (I), located on the cytoplasmic side of the inner mitochondrial membrane, exchanges coenzyme A for L-carnitine. Thus formed, acyl carnitines are shuttled across the inner mitochondrial membrane, and, at the matrix interface, are converted back to a CoA thio-ester by CAT (II). This carrier-mediated translocation is essential for ketone-body production, as D-acylcarnitine, a competitive inhibitor of acyl-carnitine translocase, can completely block ketogenesis. /17/ Smaller chain fatty acids (eight carbon lengths or less) can traverse the inner mitochondrial membrane independently of carnitine /18/; therefore, the above discussion is relevant only for longer chain fatty acids, the usual endogenous precursors for ketones.

After translocation and re-thioesterification, fatty acyl CoAs undergo progressive beta-oxidation to acetyl CoA,

which can be oxidized to carbon dioxide by way of the citric acid cycle or may be used to form acetoacetate either by direct condensation with another acetyl CoA or by cleavage of 3-hydroxy-3-methylglutaryl CoA, the quantitatively more important route. Therefore, a mechanism must exist which allows for inhibition of the citric acid cycle and concomitant accumulation of acetyl CoA. Hochachka /19/ has suggested that competition between beta-oxidation and the citric acid cycle for critical cofactors (e.g., NAD, FAD, CoASH) limits further oxidation of acetyl CoA. Alternatively, acetate entry into the citric acid cycle may be blocked by long-chain acyl CoA /20/ or ATP /21/ induced inhibition of citrate synthase or by oxaloacetate depletion (see Gluconeogenesis).

Certain amino acids--isoleucine, lysine, phenylalanine, and tyrosine /22/--can also be metabolized to ketones by virtue of acetyl CoA generation during their catabolism. Under physiologic conditions or during a brief fast, the contribution of these ketogenic amino acids to the ketone pool is probably minimal; however, if an individual is supplemented with these amines, or nutrient deprivation becomes chronic, their role becomes more prominent.

Acetoacetate and its redox mate, beta-hydroxybutyrate, are released from the liver into general circulation. The molar ratio of these compounds is dependent upon intrahepatic NADH/NAD concentrations and usually favors beta-hydroxybutyrate formation in a 3:1 ratio /23/, although a variety of medical and toxicologic conditions can shift this equilibrium. Acetone is a product of the nonenzymatic decarboxylation of acetoacetate and can be recycled by conversion into glucose. /24/

The regulation of ketogenesis appears to revolve around acyl-substrate entry into the mitochondrion. In the fed state, hepatic fatty acid oxidation and ketogenesis are inhibited, whereas *de novo* triglyceride synthesis from acetate is accelerated /25/. Insulin may directly reduce fatty acid utilization /26/; however, the principal mediator appears to be malonyl CoA /27/, the product of the first committed step in fatty acid biosynthesis. When liver glycogen /28/ and cytosolic citric acid concentrations /29/ are high (conditions known to prevent anaerobic glycolysis /30/), malonyl CoA production increases. In turn, malonyl CoA reversibly inhibits CAT (I) /18/, mitochondrial uptake of

fatty acids ceases, and newly synthesized fatty acids are diverted toward esterification to glycerol and subsequent release as VLDL.

Glucagon facilitates ketogenesis by "activating" CAT (I), resulting in an increased delivery of substrate into the mitochondrion. This effect of glucagon is indirect and involves glycogen depletion, suppression of malonyl CoA synthesis, and elevation of hepatocyte carnitine concentration. /31/

Cortisol also facilitates ketogenesis independently of its effects on lipolysis. Although the mechanism is not clear, it is reasonable to assume that this is partly due to a direct antagonism of insulin activity (see Glucose Sparing) and to augmentation of the hepatic sensitivity to glucagon.

The principal determinant influencing the shift from lipogenesis to ketogenesis is the intrahepatic proportion of insulin to glucagon. /32/ When both insulin and glucagon concentrations are suppressed, ketone synthesis is impeded. Similarly, if glucagon and insulin secretion is stimulated by a diet high in protein but low in carbohydrate, acetyl CoA is diverted to fatty-acid production and not ketogenesis. /33/ Therefore, conditions essential for ketone body formation include tight regulation of pancreatic islet cell function to assure concurrent inhibition of insulin secretion while expediting glucagon delivery to the liver.

Gluconeogenesis

Gluconeogenesis, the process of glucose production from three-carbon intermediates, occurs in both the liver and the kidney. While the liver is the principal site for gluconeogenesis, the renal proximal tubules can contribute up to 15% of the total glucose synthesis in times of maximal stress. Gluconeogenesis, like ketogenesis, is under hormonal control and regulated at the catalytic level by an elegant interplay between substrate and enzymes. Both of these regulatory mechanisms guarantee that glycolysis and gluconeogenesis do not occur simultaneously.

The major gluconeogenic precursors are alanine, pyruvate, lactate, and glycerol; however, several other amino acids, most notably arginine, aspartate, glutamate, and valine can be readily converted into glucose. /22/ Pyruvate and lactate are derived from anaerobic glycolysis in skeletal muscle, whereas glycerol is released from adipose tissue as a result of lipolysis. /10/ Striated muscle is the source of alanine; when insulin levels fall, protein synthesis declines, allowing alanine to be preferentially mobilized for hepatic utilization. /34/ The amount of alanine delivered to the liver is in excess of that which would be predicted on the basis of muscle protein composition; therefore, muscle must be capable of alanine biosynthesis. /35/ It has been suggested that pyruvate, derived from sarcoplasmic glycogen, is transaminated to alanine, simultaneously producing intermediates for the citric-acid cycle. As starvation continues, muscular glucose oxidation diminishes; consequently, pyruvate and lactate become quantitatively less important substrates and glycerol assumes a greater role.

Lactic acid, through lactate dehydrogenase, and alanine, via transamination, are rapidly converted to pyruvic acid in the liver. Pyruvate is subsequently internalized by the mitochondrion where it is acted upon by the biotin-dependent enzyme, pyruvate carboxylase, to form oxaloacetic acid. As the remainder of gluconeogenesis is a cytosolic process, and oxaloacetate is impermeable to the inner mitochondrial membrane, it must be changed to a compound capable of egress to the appropriate extra-mitochondrial compartment. This is accomplished by the enzymatic reduction of oxaloacetatic to malate and is driven by high intra-mitochondrial NADH levels from beta oxidation of fatty acyl CoA (see Ketogenesis). Malate activates the dicarboxylic acid transport protein and is ferried through the inner mitochondrial membrane. The cytoplasmic ratio of NAD/NADH is reversed and malate dehydrogenase rapidly reconverts malic acid back to oxaloacetate. /36/ Through decarboxylation by phospho-enolpyruvate carboxykinase, oxalocetate is transformed to phospho-enolpyruvate, and gluconeogenesis proceeds via a simple mass action reversal of glycolytic enzymes until fructose-1,6-diphosphate is reached. At this point, another enzyme unique to gluconeogenesis, fructose-1,6-diphosphatase, is required to dephosphorylate this compound-yielding fructose-6-phosphate, which is swiftly isomerized to glucose-6-phosphate and subsequently to free glucose by glucose-6-phosphatase.

Other amino acids can serve as glucogenic substrates by direct transamination to oxaloacetate and Z-ketoglutarate or by interconversions arising from other pathways, including the urea cycle. Examples of the former are aspartate and glutamate, while arginine is indirectly incorporated into glucose via ornithine. /37/

Glycerol enters the gluconeogenic sequence at the triose phosphate level, and consequently requires a smaller commitment of metabolic energy to be reformed into glucose.

The Cori cycle--the process of pyruvate carboxylation-decarboxylation--is absolutely essential because of the irreversibility of pyruvic acid. /37,38/ If the Cori cycle and pyruvate kinase were allowed to operate simultaneously, the cell would quickly deplete its ATP stores, because pyruvate kinase generates one ATP, whereas the Cori cycle consumes two. Hence, stringent controls must be placed on these enzyme systems. This is where hormonal and allosteric effectors play their roles to assure cellular micro-homeostasis.

The cellular and hormonal conditions associated with ketogenesis are identical to those supporting gluconeogenesis. In essence, both pathways can mutually reinforce each other (Figure). With low insulin levels and elevated glucagon concentrations, hepatocyte cAMP production is increased, resulting in phosphorylation and subsequent inactivation of pyruvate kinase. /36/ Alanine also reversibly inhibits this step. /39/ A decrease in circulating insulin plus high mitochondrial concentrations of acetyle CoA (from beta oxidation) serve to halt the enzymatic decarboxylation of pyruvate acid by pyruvate dehydrogenase /40,41/ and allosterically activate pyruvate carboxylase. /39/ These events channel pyruvate into oxaloacetate synthesis and ensure that the Cori cycle does not become the "futile" cycle. Disposal of oxalacetate through the citric acid cycle is prevented by inhibition of citrate synthase due to activity of beta-oxidation (see Ketogenesis); therefore, oxaloacetic acid is uniformly directed into malate production. The remaining irreversible steps of glycolysis, hexokinase, and phospho-fructokinase can be inhibited by free fatty acids if the intracellular concentration of these lipids exceeds the capacity of their binding proteins. /42,43/

Cortisol can profoundly influence gluconeogenesis by induction of transaminase, phospho-enolpyruvate carboxykinase, and fructose-1,6-diphosphatase /36-44/, thereby reinforcing the machinery responsible for glucose production. Glucocorticoids (in association with insulin deficiency) also sustain gluconeogenesis by promoting protein wasting, resulting in an accelerated delivery of glucogenic amino acids to the liver. /35/ In addition, cortisol enhances the activity of the urea cycle /44/, which indirectly adds more potential substrates for gluconeogenesis.

Glucose Sparing

Several days are required for the CNS to completely adapt to ketone body utilization. /8,35/ Prior to this adjustment, neuronal energy needs are provided by glucose oxidation. As a result, a variety of mechanisms are employed to prevent peripheral glucose uptake, thus sparing it for CNS consumption.

Although the initial, and most obvious, glucose-sparing effort is prompt suppression of insulin secretion, reduction in insulin levels alone is probably insufficient to insure against neuroglycopenia because ketones may enhance insulin tissue binding /45/, and other factors, such as exercise /46/, will lower blood glucose concentrations. Therefore, additional measures must be operating to conserve carbohydrates, and, like the other biochemical alterations unique to fasting, involves a combination of both hormonal and substrate-level counter-regulation.

As insulin levels fall, there is a reciprocal rise in tissue binding secondary to an up-regulation in the number of receptors. /47/ Glucocorticoids interfere with this phenomenon by reducing both insulin receptor number and affinity. /48/

Besides inhibiting insulin secretion, epinephrine has been shown to reduce glucose tolerance by antagonizing the peripheral actions of insulin. /49/

Growth hormone is also crucial in shifting metabolism from the post-absorptive state to fasting and, beside its actions on lipid mobilization or gluconeogenesis, may impair glucose disposal by reducing peripheral insulin responsiveness. /50/

Alternate substrates, i.e., fatty acids or ketones, also play a prominent role in glucose sparing. /51/ Free fatty acids can inhibit key glycolytic enzymes, and acetyl CoA, originating from the oxidation of either ketone bodies or fatty acids, checks the activity of pyruvate dehydrogenase. In extrahepatic tissues where the citric acid cycle remains in operation, citrate may be transferred out of the mitochondrion and can allosterically inactivate phospho-fructokinase /52/, adding another block to glycolysis. The ultimate outcome of these modulations in enzyme activities is the production of an insulin postreceptor defect which prevents efficient glucose uptake.

Another consequence of the "glucose-fatty acid cycle" /51/ is the preservation of glycogen reserves in both liver and muscle. Although the total amount of glycogen in the body is small, it does provide an excellent acute defense against hypoglycemia.

Chronic Adaptions

Thus far, this discussion has centered around the hormonal and substrate alterations that occur during brief starvation. Adaptation to protracted nutrient deprivation continues throughout the course of fasting and is manifest primarily by a diminution in the magnitude of nitrogen deficit. This attempt at protein conservation seems teleologically appropriate in that, as the brain becomes more proficient in metabolizing ketones, the need for gluconeogenesis, hence the rate of protein catabolism, falls and amino acids can be recycled for cellular remodeling or *de novo* protein synthesis.

The data abstracted by Ruderman /35/ suggest that the rate of gluconeogensis and urinary nitrogen excretion peaks at 2-4 days after fasting begins, and, if expenditure of muscle protein continued at such a pace, the average human

would exhaust his protein resources in just 2 weeks. After approximately 4 days, blood levels of amino acids decline, as does hepatic glucose production. This effectively extends the potential utilization of muscle protein for an additional 2 months. /35/ The mechanism for stabilization of the body's protein pool is not completely understood; however, it has been shown that infusions of either ketones or keto acid analogs of branched chain amino acids can promote nitrogen sparing. /53,54/ Indeed, available data /35/ suggest an inverse relationship between serum ketones and the amount of urinary nitrogen excreted during periods of prolonged starvation.

Receptor affinity for insulin increases during periods of fasting, and, although there is conflicting information /55/, ketones may be acting to preserve protein through facilitation of the binding of insulin to issues. /45/ As Glass and collegues /56/ have demonstrated, the effects of insulin on glucose uptake can be dissociated from its actions on branched chain amino acid disposal and may imply that the insulin post-receptor defect present in starvation /52/ is limited to glucose oxidation. Under these circumstances, insulin could exert a positive influence on protein synthesis/sparing without appreciably altering carbohydrate homeostasis. Other hormones, such as growth hormone, may also mediate protein conservation.

An additional adaptive mechanism for survival is a marked reduction in basal caloric expenditure /57/. Coexistent stress (malignancy or sepsis) may negate this phenomenon /58/, resulting in caloric consumption exceeding that associated with physical activity.

PHYSIOLOGIC LIMITATIONS

Nutrient storage pools are not limitless, and common sense dictates that exhaustion of these reservoirs would be fatal. Depletion of one-third to one-half of muscle protein content appears to be the limiting factor in some models /35/, but others /59/ argue that exhaustion of body fat is the more critical determinant. Nonetheless, by basing their calculations upon the experience of the IRA

hunger strikers, Leither and Marliss /59/ have estimated the average survival during total starvation in otherwise normal males to be 60 days.

SUMMARY

Nature provides economical methods of fuel storage and prudently orchestrates nutrient utilization by a complex interplay between hormones, capable of furnishing coarse regulation, and substrates or their metabolites which supply the fine tuning. While these mechanisms are adaptive in the short run, long-term starvation can disrupt the means of adjustment, which would result in organ failure and eventual death. The principal objective of nutritional support is to support the patient in times of crises by restoring macro-and micronutrients.

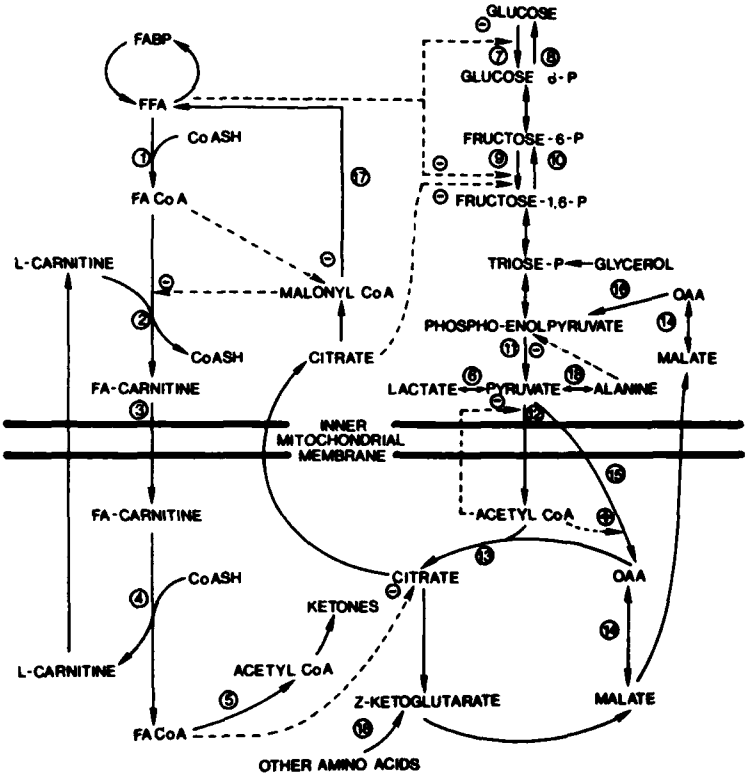

Figure. Interrelationship between ketogenesis and gluconeogenesis. (Many intermediate reactions have been omitted for clarity.) The solid lines indicate the direction of substrate flow and the dashed lines show the sites of substrate-level enzyme inhibition (–) or stimulation (+).

Abbreviations: CoASH = coenzyme A; FFA = free fatty acid; FABP = fatty acid–binding protein; OAA = oxaloacetic acid.

Enzyme key: (1) Fatty acid: CoASH ligase (AMP); (2) Carnitine acyl transferase (I); (3) Acyl carnitine translocase; (4) Carnitine acyl transferase (II); (5) Beta oxidation; (6) Lactate dehydrogenase; (7) Hexokinase; (8) Glucose–6–phosphatase; (9) Phosphofructokinase; (10) Fructose–1, 6–diphosphatase; (11) Pyruvate kinase; (12) Pyruvate dehydrogenase complex; (13) Citrate synthase; (14) Malate dehydrogenase; (15) Pyruvate carboxylase; (16) Phospho–enolpyruvate carboxykinase; (17) Fatty acid synthetase complex; (18) Transaminases.

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Figure. The Four Horsemen

INFECTIOUS CONSEQUENCES OF MALNUTRITION

LTC David R. Haburchak, MD, MC

Since antiquity, man has observed the interrelationship of famine and plague. As symbolized in Duerer's woodworking (Figure) the four horsemen ride side by side, Plague at the front with his arrows of pestilence, War close by his side, followed by Famine and Death. The relationship between Plague and Famine is not clearly one of cause and effect. Rather it appears to be interactive, at times synergistic, at times antagonistic; certainly, it is more complex than first appearance suggests.

This paper will attempt to describe infectious consequences of total caloric malnutrition as exhibited in population studies, animal models, immunological parameters and clinical practice.

Population Studies

In 1968, Schrimshaw et al /1/ reviewed 484 studies of animals and man to conclude that preexisting malnutrition increased the severity of acquired infection, and infection itself worsened preexisting nutritional deficits. Gastrointestinal and respiratory diseases, in particular, appear to be of increased frequency and severity in the undernourished. Bacterial infections appear to be more consistently worsened by total caloric malnutrition than viral infections.

Some infectious illnesses, however, appear to be antagonized by malnutrition and, in fact, are worsened by refeeding. /2/ This phenomenon is most clearly documented in the studies of the Murrays in the Sahel. /3/ These authors showed that certain critical elements, most notably iron and selenium, may be more advantageous to the parasite than to the host; refeeding iron-supplemented grains caused significant exacerbation of measles, tuberculosis, and malaria. This phenomenon has been explained by saturation of previously

depressed host iron-binding capacity by the exogenous iron, thereby allowing free iron for the parasite. /4/

Historical data from World War II suggests that the malnourished peoples of occupied Europe and the internees of concentration camps did not suffer excessive infectious mortality. /5/ In particular, typhus epidemics in Eastern Europe were confined to well-fed prison guards rather than starved prisoners. /4/ One notable exception was an increase in Pneumocystis infections seen in children of that time.

Additional support for an antagonistic relationship between malnutrition and infection comes from the near-universal symptom of anorexia associated with infections. /5/ Teleologically, such universal phenomena as fever and anorexia would be expected to have selective advantage for the host. While this may have once been true, today's hospital infections certainly are not those of evolutionary importance, and any universal extrapolation that anorexia is good would be patently absurd.

Animal Models

Histopathologic and survival studies of animals have uniformly shown a strong synergistic relationship between infection and total caloric or dietary component deficiency. Although the host histopathology appears similar for deficiencies of total calories, proteins, vitamin B_6 or iron, the response to different challenge organisms is impressively different, once again suggesting that the liability of malnutrition to the host may be somewhat dependent upon the parasite encountered.

A common morphologic finding in animal malnutrition is involution of the thymus and thymus-dependent areas of the lymph nodes and spleen. /6/ Paracortical periarteriolar areas are depleted of small lymphocytes, and in cases of severe malnutrition, germinal centers may be scant. Tonsils and IgA-secreting lymphoid tissue of the gut may also be suppressed. The lymphoid hypoplasia may be a direct result of the malnutrition, or mediated through the increased cortisol levels that occur with malnutrition.

Immunologic Parameters

The Table summarizes the effects of caloric malnutrition on a number of immunologic parameters measured in both animals and humans. /6-8/ The wide breadth of impact can be immediately appreciated. The cell-mediated and phagocytic immune systems appear most impaired, suggesting a heightened susceptibility to bacterial and fungal infections and appearing to confirm the population studies described.

Specific dietary deficiencies have been shown to have an effect on certain immunologic parameters: Iron deficiency depresses bactericidal activity of leukocytes and cell mediated immunity, and zinc deficiency is becoming increasingly recognized as a cause of cutaneous infection and depressed cellular immunity. Vitamins A, C, and riboflavin also are important for maintaining epithelial integrity. /8/

Clinical Practice

Since the 1940s, investigators have demonstrated increased postoperative morbidity associated with objective parameters of malnutrition. /9/ The significant clinical parameters of malnutrition that predict postoperative complications are as follows: /10/

Clinical Parameters	Risk over Control
Serum albumin < 3 gm%	2.5 times risk
Transferrin < 220 mg/dl	5 times risk
Anergy	2,5 times risk

In this series /9/, anergic patients had a 33% complication rate.

Unfortunately, it is extremely difficult to show that improving nutrition has substantial impact on prevention of infection. Field studies, in particular, are difficult to control. /11/ Theoretically derived fad diets and non-physiologic doses of vitamins have not been supported by well-controlled studies of their implementation. /12/

CONCLUSION

At present, there is no universal elixir for preventing infection. Optimum health is achieved through optimum well-balanced nutrition and maintenance of physiologic levels of calories, proteins, and vitamins. While the course of bacterial and fungal infections appears to be adversely affected by malnutrition, certain deficiency states may, in fact, benefit the host during certain infections. Theoretical and experimental evidence exists for such an antagonistic relationship between malnutrition and some viral, metazoan, and protozoan infections. Since bacterial and fungal infections pose the greatest risk to patients in today's hospitals, physicians should prospectively assess the nutritional status in all of their patients. Maintenance of an adequate nutritional state is the hospitalized patient's best protection from most common hospital-acquired infections.

TABLE

INFLUENCE OF CALORIC MALNUTRITION ON HOST IMMUNOLOGIC PARAMETERS

Humoral Immunity

IgA, IgM, IgG, IgD, IgE - elevated in most malnourished individuals; may represent exposure to recent infections.

Secretory IgA - depressed.

Response to Immunizations - Depressed in direct proportion to amount of protein deprivation. Usually adequate, but quite variable. Typhoid is most consistently depressed.

B Cell Population - circulating levels normal.

Cell-Mediated Immunity

Skin Test Response - Depressed
T-Cell Population - Depressed
Null Cells - Increased
Mitogenic Response - Depressed; recovers with refeeding.

Phagocytosis

Chemotaxis - normal
Phagocytic ingestion - normal
Killing - depressed

Other Factors

Complement levels - reduced, consumed
Opsonic function of plasma - normal
Skin change - barrier defenses decreased

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MINERALS, VITAMINS, AND TRACE ELEMENTS IN PARENTERAL NUTRITION

LTC Robert L. Myers, MD, MC

To be nutritious, food must provide minerals, vitamins, and some trace elements, as well as adequate calories, distributed proportionately among the three basic energy sources (carbohydrates, fat, and protein). Presently, calcium, magnesium, and phosphorus, four fat-soluble and seven water-soluble vitamins, and some trace elements are considered essential. A brief consideration of the requirements and deficiency syndromes, and a practical approach to supplying these materials follows.

CALCIUM, MAGNESIUM, AND PHOSPHORUS

Calcium. Large stores are present and homeostatic mechanisms provide tight control of blood levels. Because stores of calcium may be mobilized in the bedridden patient, supplements must be give with care or not at all. Rapid phosphate infusion may precipitate hypocalcemia and require supplemental calcium infusion.

Magnesium. This divalent cation is required for activation of many enzyme systems, and symptoms may develop as serum levels approach 1 mEq/L. Magnesium deficiency is indistinguishable from hypocalcemia (positive Trousseau's and Czvostek's signs, spasticity, weakness, psychosis, nausea) except for serum levels and electrocardiographic changes of depressed ST segments and T wave inversion in hypomagnesemia, and prolonged QT intervals in hypercalcemia. /1/ Magnesium deficiency may promote potassium loss, antagonize repletion of calcium, and enhance phosphaturia. Depletion is commonly seen in alcoholics and patients with gut disorders (short-bowel syndrome, starvation, fistulas), as well as in some patients with renal diseases. Therapy consists of magnesium sulfate, 0.35-0.45 mEq/kg/day. /2/

Phosphorus. Ubiquitous in body energy metabolism, phosphate depletion can present as rhabdomyolysis, hemolytic

anemia, weakness to the point of hypoventilation, reduced resistance to infection, and platelet dysfunction. /3/ Causes for deficiency include alcoholism, alcohol withdrawal, parenteral nutrition (especially at the outset of anabolism), alkalosis, and aluminum antacids. Daily needs vary; generally, 7-9 mmoles/1,000 kcal is recommended, with adjustment as dictated by serum levels, degress of stress, and severity of catabolism. Each 1,000 cc of LIVN solution provides 419 mg of elemental phosphorus (13-14 mmoles/L).

VITAMINS

Vitamin requirements as they pertain to parenteral nutrition are as follows:

1. Fat-Soluble Vitamins. The fat-soluble vitamins include vitamins A, D, and K. The half-lives are unusually long (600 days for vitamin A), and deficiencies are relatively rare. However, patients needing TPN often have inadequate vitamin intake before alimentation, particularly if malabsorption blocks uptake. Stress may also accelerate need.

a. Vitamin A. Body stores lasting 3-12 months are normally present. Nyctalopia (night blindness), xerophthalmia, and skin eruptions suggest a vitamin A deficiency.

b. Vitamin D. Inadequate stores of vitamin D lead to impaired bone mineralization. The major role of vitamin D is to facilitate calcium and phosphorus absorption across the gut; some argue that it should not be given at all during TPN. The RDA is included in LIVN.

c. Vitamin E. Thrombotic events, mild anemia (because of decreased red-cell survival), and myopathy characterize vitamin E depletion. Unsaturated fatty acids increase requirements, and extra amounts of vitamin E should be given when fat emulsions are administered.

d. Vitamin K. Vitamin K depletion leads to inadequate prothrombin complex and bleeding tendencies. Vitamin K should be given intramuscularly once a week.

2. Water-Soluble Vitamins. Water-soluble vitamins have lower tissue stores and are more easily depleted by stress than fat-soluble vitamins; thus, while fat-soluble vitamin replacement is optional, water-soluble replacement is mandatory. Prompt renal excretion prevents toxic levels of water-soluble vitamins from accumulating.

a. Vitamin B_1. Wernicke's encephalopathy with disturbed consciousness, paretic extraocular muscles, nystagmus, high output congestive heart failure (wet beriberi), and myoneuropathies have all occurred in patients receiving TPN without thiamine. Requirements increase as calorie infusion increases; 0.5 mg/1,000 kcal is needed.

b. Vitamin B_2. Cheilosis, conjunctivitis, and sebhorrheic dermatitis may occur within 7 days following a riboflavin-free diet.

c. Vitamin B_5. Insufficient niacin may lead to a painful tongue, anorexia, lassitude, and indigestion. Hyperpigmented dermatitis of sun-exposed skin and diarrhea follow. Toxic confusional psychosis completes the picture of pellagra.

d. Vitamin B_6. Personality changes, stomatitis, acneiform rashes, and microcytic hypochromic anemias characterize pyridoxine deficiency, which may occur within 3 weeks of a vitamin B_6 deficient diet.

e. Folate/B_{12}. Ordinarily stores of both folate and vitamin B_{12} are so large that depletion is of little concern, and standard vitamin solutions are adequate to prevent megaloblastic changes.

f. Vitamin C. Ascorbic acid is especially important in connective tissue metabolism. Scurvey, characterized by anemia, mucosal hemorrhage, and gingivostomatitis, is caused by vitamin C depletion. Symptoms develop in 20-30 days and are dramatically accelerated by major burns or trauma. Normally, 45 mg/day of vitamin C is needed; following severe injury, up to 300 mg/day be required. /4/

RECOMMENDATIONS

1. Vitamins, like trace elements, are adequately supplied by enteral nutrition as long as 1,500-2,500 kcal/day are given. Supplemental vitamins need only be given if partial enteral alimentation is done.

2. At LAMC, MVI-12, 10 cc/day, provides the RDA as suggested by Blackburn and the AMA. /5/

3. Stores of fat-soluble vitamins may accumulate; therefore, the RDA should not be exceeded. On the other hand, stress may increase the need for water-soluble vitamins. Excesses are excreted harmlessly in the urine. Extra amounts for severely ill patients may be given as Berroca-C.™

TRACE ELEMENTS

Presently, 15 trace elements are believed to be essential for the mammalian diet. /2/ Before the advent of parenteral nutrition, trace element-free diets were difficult to select, so that depletion states were poorly defined. With long-term nutritional support, more information will be available about recommended daily allowance (RDA) and means of replacement. In discussing trace elements, only deficiency states will be considered. The RDAs, dosing levels, and serum levels are shown in the table at the end of this article.

Cadmium, Cobalt, Fluorine, Nickel, Tin, Vanadium, and Silicon. Deficiency states are known in animals, but not in man. No RDAs have been established.

Selenium. A convincing case of cardiomyopathy associated with prolonged TPN and low selenium levels was recently described. /6/ This example suggests that depletion states may eventually be described for all of the above elements.

Chromium. Apparently, normal glucose use requires enough chromium to facilitate insulin-receptor interaction. Glucose intolerance to the point of diabetic neuropathy may result from depletion.

Copper. Hypochromic hypoproliferative anemia, leukopenia, and hypoproteinemia may result from low levels of copper. Copper, like iron, is essential for hemoglobin synthesis and cytochrome oxidase function. It also plays a role in connective tissue integrity so that depletion may lead to bone changes resembling scurvey.

Iodine. Prolonged iodine-free diet may lead to goiter.

Iron. Low stores of iron cause anemia. Iron may be added to TPN solutions, but usually is given monthly as parenteral iron dextran.

Manganese. Deficiency presents as dermatitis, hair color change, hypocholesterolemia, glucose intolerance, and possible skeletal changes related to its role in activating chondroitin sulfate synthesis.

Zinc. Zinc is called "the trace element of the year." Zinc depletion is well recognized and may occur after 2-3 weeks of zinc-free alimentation. It presents as diarrhea, followed by alopecia and a scaling, peristomal, intertriginous dermatitis. Depression, impaired wound healing, and a decreased sense of taste may also occur. Cirrhosis, diarrhea, malabsorption, and steroid therapy predispose to zinc depletion.

In general, the following guidelines apply to trace elements:

1. Enteral provision of 1,500-2,500 kcal/day by standard oral feeding solutions gives adequate amounts. Little supplementation is needed.

2. Only zinc and copper are supplied in standard parenteral solutions at LAMC, as is the practice at many medical centers. Serum copper and zinc levels should be measured weekly.

3. With any of the trace elements, gut control of absorption is bypassed; therefore, care must be taken to avoid giving toxic amounts.

TABLE 1

VITAMINS, MINERALS, AND TRACE ELEMENTS:
REQUIREMENTS AND AMOUNTS PROVIDED IN LIVN

Additive	Recommended Daily Allowance*	Units/Day of LIVN†
Fat-soluble vitamins		
A (IU)	3,300	3,300
D (IU)	200	200
E (IU)	10	10
K (mg)	5 mg (given parenterally weekly)	
Water-soluble vitamins		
B1 (mg)	3	3
B2 (mg)	3.6	3.6
B3‡ (mg)	15	15
B5 (mg)	40	40
B6 (mg)	4.0	4.0
B12 (mμg)	5	5
C (mg)	100	100
Folate (mμg)	400	400
Minerals		
P (mmoles/1000 kcal)	7-9	13-14
Mg++ (mEq/kg/day	0.35-0.45	8 mEq
Ca++ (mEq/kg/day)	0.2-0.3	5 mEq
Fe (mg)	0.5-2.0	
Zn (mg)	1.0-2.2	2.0
Cu (mg)	0.63-1.78	0.4
Other trace elements	RNAs not established and not supplied in LIVN	

*As recommended by Blackburn and American Medical Association.
†Provided per 24 hr independent of volume infused.
‡Deficiency states not recognized and RDAs not established.

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REFLECTIONS

"When a man's stomach is full, it makes no difference whether he is rich or poor" (Euripides, Electra, 412 B.C.).

"A man seldom thinks with more earnestness of anything than he does of his dinner" (Samuel Johnson, 1786).

"He who distinguishes the true savor of his food can never be a glutton; he who does not cannot be otherwise" (Thoreau, Higher Laws, Walden, 1854).

"One cannot think well, love well, sleep well, if one has not dined well" (Virginia Woolf, A Room of One's Own, 1929).

"Neither salt nor advice should be given unless asked for" (Benjamin Franklin).

"I'm not going to starve to death just so I can live a little longer" (Irene Peter).

"An empty stomach is not a good political adviser" (Albert Einstein).

"Principles have no real force except when one is well fed" (Mark Twain).

PERIPHERAL PARENTERAL NUTRITION

CPT Robert H. Peters III, MD, MC

The use of peripheral parenteral nutrition (PPN) has indications that vary from those for central total parenteral nutrition (TPN). In general, PPN is useful in those patients who for various reasons are unable to take food by mouth, or whose intestines are not functioning for short periods of time, i.e., 7-10 days. The main indications and contra-indications for PPN are shown in Table 1. In some situations where TPN is necessary, PPN can meet total nutritional needs if close attention is paid to management of PPN; however, in most cases, PPN can provide only about 2,000 calories per 24 hours.

Venous access is obtained using a 20- to 22-gauge flexible venous catheter in a generous-sized peripheral vein. On an upper extremity, initial catheter insertion sites should be as distal as practical. It is necessary to change the site every 24-36 hours to avoid irritation to the vein and to retain the vein for later use. The use of OPSITE™ for dressing the puncture site allows inspection of the skin around the site without removing the dressing. The catheter site should be changed at the first sign of inflammation.

PROTEIN-SPARING THERAPY

For the last four decades, 5% dextrose has been used in an attempt to spare protein in postoperative patients by lowering the requirement for gluconeogenesis. In the early 1970s, several investigators began using amino acid solutions to prevent negative nitrogen balance in patients who were unable to use enteral alimentation. Blackburn et al /1/ have shown that, in the presence of high insulin levels, lipolysis from endogenous fat provides an efficient energy source. The infusion of amino acids in concentrations up to 5% is usually well tolerated by the patient. /2/ Available is a 3.5% amino acid solution with added electrolytes which, when given at the rate of 3 liter/day, provides 105 gm of protein. Additional

electrolytes, vitamins, or trace elements can be added to this preparation. Table 2 details the formulation of this standard amino acid solution.

Initial infusion is begun at 1 liter/day. This rate may be increased by 1 liter/day to 3 liter/day. The limitations of peripheral amino acid therapy are related to volume (CHF, renal failure, and fluid overload) and the handling of amino acids (hepatic failure and renal failure). Patients on nutritional alimentation require close observation for toxicity related to this therapy.

Again, it should be emphasized that this therapy is indicated in those patients who exhibit no nutritional deficits or who are minimally deficient, and in whom return of bowel function is expected in a short time.

LIPID SYSTEM

Over the last 20 years, a product has become available which allows the physician to use an isotonic solution, i.e., capable of being infused peripherally to replace glucose as a nonprotein energy source. In the 1950s, a cottonseed oil emulsion (Lipomul®) was tried, but it was found to produce fever, coagulation defects, and jaundice. Since 1961, 10% soybean oil emulsified with 1.5% egg yolk phospholipid, and 2.5% glycerol to obtain isotonicity has been in use. This preparation has a low reported incidence of side effects. /3,4/

Soybean oil appears effective for several reasons: The mean particle size is the same as chylomicrons (0.13μ); the pH of the emulsion approximates blood pH 7.4; and the lipid emulsion appears to have a local protective effect on the vascular endothelium. Lipid emulsions provide a concentrated energy source, i.e., 9 kcal/gm as compared to glucose 4 kcal/gm. /5/

The tolerance of lipid emulsion appears to be about 2-4 gm/kg of body weight per day, or 140-280 gm/day for a patient weighing 70 kg. Toxicity associated with soybean oil emulsions is low. A study of 292 pediatric patients in whom soybean emulsion accounted for at least 35% of the calorie

intake reported two side effects in 133 adults and 12 side effects in 159 pediatric patients. The side effects associated with pediatric patients all occurred at doses greater than 4 gm/kg body weight per day. The side effects in adults were elevation in SGOT, SGPT, and alkaline phosphatase, and feelings of tiredness and sleepiness during infusion. Reports of thrombocytopenia are rare.

When using lipid emulsion as a nonprotein calorie source in PPN, the amino acid solution is infused concurrently with a lipid emulsion, allowing a higher concentration of amino acids to be used without causing local venous irritation or thrombophlebitis. The Y connector, which is placed immediately before the venous catheter, mixes the hypertonic amino acid solution with the isotonic lipid emulsion. The IV site should be changed every 24-36 hours to preserve the vein for future use.

The lipid emulsion flows slower than the amino acid solution. Rate control is more accurate if an infusion pump is used with the lipid emulsion bottle. Both bottles should run continously. If the amino acid is allowed to run without lipid running, vein irritation will occur. The lipid emulsion should be started alone at a slow rate to determine any immediate hypersensitivity such as rash, dyspnea, chest or back pain, dizziness, cyanosis, or headache. Serum triglyceride levels should be measured within a few hours of initiating infusion to look for intolerance to lipid therapy.

Administration of 1500 ml of a 5.9% amino acid solution with 10% glucose and electrolytes and 1500 ml of 10% lipid emulsion provides 3000 ml of water, 87.9 gm of protein, and 2250 nonprotein calories. Any additional electrolytes, vitamins, or trace elements should be added to the amino acid bottle. Nothing should be added to the lipid emulsion. The IV tubing used with the lipid should not have a filter, since the particle size of the lipids would be trapped.

The use of the lipid system should be reserved for use by patients who are under minimal stress and who, following nutritional evaluation, demonstrate minimal deficiencies. As with other forms of nutritional support, PPN requires close monitoring. This system is especially helpful in patients who cannot tolerate a carbohydrate load, since the primary calorie source is fatty acids.

The contraindications to the lipid system are related to volume (CHF, renal failure) and the handling of lipids (hyperlipidemias and severe liver failure). The limitations of amino acid therapy also apply.

TABLE 1
MAIN INDICATIONS AND CONTRAINDICATIONS FOR PPN

	Indications	Relative Contraindications
Protein Sparing:	Inadequate oral intake	Enteral route available
	Marginal nutritional status	Peripheral vein not available
	Brief period of starvation anticipated	Prolonged use greater than 7-10 days
	Indications for TPN not absolute	Increased or excessive nutritional requirements
Lipid System:	Nutritional support required	Enteral route available
	Central vein not available	Peripheral vein not available
	Carbohydrate intolerance	Liver disease
	Fluid restriction	Lipid disorders

TABLE 2
COMPONENTS OF THE 3.5% AMINO ACID SOLUTION PER LITER

L-amino acids	3.5 gm
Total nitrogen	588 mg
Approximate pH	6.0
Osmolality	450 mOsm/liter

Electrolytes

Sodium	25 mEq/liter
Potassium	15 mEq/liter
Magnesium	5 mEq/liter
Acetate*	54 mEq/liter
Chloride	25 mEq/liter
Phosphate (as HPO_4)	15 mEq/liter

*Acetate is added as sodium acetate and as acetic acid for pH adjustment.

TABLE 3
COMPONENTS OF THE LIPID SYSTEM

Bottle A

500 ml 10% lipid emulsion

Bottle B

500 ml 5.95% amino acid - 10% glucose

Additives (per 500 ml):

Sodium (as acetate)	45 mEq
Potassium (as chloride)	40 mEq
Magnesium (as sulfate)	8 mEq
Calcium (as gluconate)	5 mEq
Multiple vitamins	5 ml/day

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ENTERAL ALIMENTATION: CLINICAL ASPECTS

MAJ Floyd Burton, MD, MC

The most common problem in nutritional management of seriously ill patients is not that they cannot eat, but that they cannot willfully eat enough. /1/ Thus, anorexia is the major cause of protein-calorie deficiency. Enteral hyperalimentation is any means of increasing delivery of nutrients to the gut for absorption, either through oral intake or tube feedings.

Tube feedings, used since the time of the Romans, were first described in 1882, with the tube being placed by "four stout men" at each feeding. /2/ In the 1950s, the Barron pump was designed to ensure accurate flow rates of a viscous tube feeding formula, basically a blenderized diet. The 1970s saw a proliferation of various formulas, each with specific indications.

PHYSIOLOGY

A number of physiologic changes may occur in the gastrointestinal (GI) tract during starvation. These changes may be reversed with resumption of gut use through enteral feedings. Gastric emptying occurs at a fairly even rate, whether nutrition is supplied by table food, blenderized tube feeding, or an elemental diet, except in severely hyperosmolar elemental diets, when gastric emptying may be slowed. Results of studies of pancreatic secretion are conflicting, but pancreatic volume and bicarbonate appear to vary with flow of gastric acid into the duodenum, whereas enzyme or protein output is sustained at a high level postprandially, independent of duodenal acidification or pancreatic bicarbonate secretion.

Animal studies show that luminal nutrition is needed to maintain the structural and functional integrity of the small intestine. Intravenous feeding of rabbits is associated with a slowing of epithelial cell proliferation and a loss of mucosal cell thickness in the proximal small bowel. /3/ Rats

fed intravenously develop a lower gut weight, decreased mucosal thickness, and less mucosal protein, DNA, and disaccharidase activity than orally fed control rats. /4/ The GI tract is already atrophic, being subnormal both in structure and function in cachectic patients. The use of intravenous alimentation as the sole route of nutrition causes involutional changes that may worsen the problem. Humoral changes are most likely responsible for these morphologic abnormalities. /5/

As refeeding is begun, the bowel resumes its absorptive function. Usually 24-36 hours of feeding is required before the minimum daily requirement of foodstuff can be absorbed. This is part of the rationale for gradual resumption of enteral feeding.

INDICATIONS FOR ENTERAL ALIMENTATION

When nutritional support becomes necessary, the route of alimentation must be selected. Options include: (1) oral feeding; (2) oral nutritional support; (3) enteral tube feeding; (4) intravenous nutritional support; or (5) a combination of the above.

Feasibility of enteral nutrition depends on the presence of sufficient functioning bowel to allow absorption of nutrients. Specific investigations are usually not indicated to determine the extent of functioning bowel, although patient history and standard laboratory data may provide an estimate. Most patients tolerate standard tube feedings well.

Patients in need of oral or enteral nutritional supplementation are those in whom: /6/

1. Spontaneous oral consumption is insufficient. Patients with anorexia, weakness, and lethargy from chronic disease, nausea from chemotherapy, oral inflammation from carcinoma or trauma, and increased nutritional requirements such as sepsis, multiple traumas, or severe catebolism are good examples.

2. Oral consumption is contraindicated. Patients with certain neurologic disorders and decreased level of consciousness

as in stroke, coma, or stupor, certain oropharyngeal or esophageal disorders as with obstructing lesions or dysphagia are examples. Some patients with fistulas, inflammatory bowel disease, or malabsorption may also be candidates for oral or enteral nutritional supplementation.

3. Specific nutritional requirements are indicated. Some patients with cardiac, renal, or hepatic failure may benefit from or require dietary restrictions or special supplements. Oral nutritional supplements may suffice in patients with normal nutritional status and increased nutritional needs, or in patients with mild protein-calorie malnutrition and normal or increased nutritional requirements. Frequently, however, portions of the upper alimentary tract must be bypassed, even though the small bowel and/or colon may be functioning well. Tube feedings into the stomach duodenum, or jejunum can be used in patients having difficulty in swallowing, increased nutritional needs, or moderate-to-severe protein deficiency.

A feeding gastrostomy or jejunostomy may be useful to bypass an oral or upper GI obstruction, an upper GI fistula, or to provide chronic enteral nutritional support.

CONTRAINDICATIONS

Enteral nutrition is not indicated for all patients. Specific contraindications include:

1. Previous unsuccessful trials of enteral nutrition.

2. Early short-bowel syndrome.

3. Certain medical illnesses, e.g., peritonitis, acute intestinal obstruction, mid-intestinal fistulas, paralytic ileus, severe malabsorption, GI hemorrhage, vomiting, or intractable diarrhea.

FEEDING TUBES

A variety of feeding tubes are available. Traditionally, a 16-18 F Levin-type nasogastric tube has been used. This tube has proved to be extremely irritating, frequently causing pharnygitis, sinusitis, otitis, and pressure necrosis of the nares, especially when an endotracheal tube is in place. The large size of the nasogastric tube causes gastroesophageal reflux, increasing the risk of aspiration or esophagitis. Smaller, more flexible nasogastric feeding tubes are now available. These tubes are usually made of polyurethane or silicone rubber that will not stiffen when exposed to gastric juices, and therefore can be left in place for weeks to months.

Most types of feeding tubes have a radio-opaque stripe or several markers to facilitate tip-location under fluoroscopy. All have some type of metal weight (most have elemental mercury) at the tip, easing passage into the intestine and serving to anchor the tube. While various lengths are available, a 36-inch tube is satisfactory for gastric feeding. For transpyloric feeding, a 42-inch length is required. Always use the smallest tube through which the formula will flow, thereby reducing gastroesophageal reflux and damage to the nares. Size 10 F allows passage of the more viscous formulas, which thinner formulas may pass through a 5 F or a 6 F tube. A pump may be needed to push the more viscous formulas through a small tube.

Feeding-tube insertion is similar among alert cooperative patients, /7/ Place the patient in a sitting position and select the more patent nostril. Lubricate the stylet as instructed on the feeding tube package and insert through the feeding tube. (A small amount of mineral oil may be useful.) Lubricate the distal 10 cm of the tube (do *not* use mineral oil here, as you risk a lipid pneumonia). Aim the tube posteriorly and downward. With the tube in the posterior nasopharynx, rotate it 180 degrees. Continue advancing the tube while the patient swallows repeatedly. Sips of water may help the patient.

In patients unable to swallow, the stylet may produce enough stiffening to allow the tube to be pushed through the oropharynx. If this cannot be done, the feeding tube can be

wedged into half a gelatin capsule using a 16 F Levin tube. The Levin tube can then be passed into the stomach. The feeding tube is separated by injecting water down the tube or by waiting 30 minutes until the capsule dissolves, at which time the tube may be removed.

Feeding tubes are conveniently marked to aid in determining the length of insertion. An easy method is to measure from the tip of the nose, to the ear lobe, to the xyphoid process. This should place the feeding tube in the body of the stomach. The normal distance from the cardia to the duodenum is 15 cm; insertion of 65-70 cm of tube should place the tip near the pylorus. To confirm placement in the stomach, aspirate the gastric contents and assure a pH of less than 4.0. Introduce air through the feeding tube while auscultating over the stomach to indicate location of the tip. Fluoroscopy or an abdominal flat plate should be used after all nasoenteric tubes to confirm proper placement. Allow sufficient time (about 4 hours) for the tube to pass from the stomach into the bowel before obtaining an x-ray.

Misplacement of the feeding tube tip can produce serious, sometimes fatal, complications in patients already debilitated. If the tube coils in the esophagus or has not been advanced into the stomach, the feeding formula accumulates in the esophagus, and regurgitation, aspiration, or infusion into the lungs may occur. Coiling of the tube in the stomach with the tip in the fundus predisposes the patient to aspiration. Inadvertent passage of the tube from stomach into duodenum may lead to diarrhea, pain, or weakness during feedings, especially with bolus feedings.

Optimum tube placement depends on the condition of the patient. The tip should never be left in the esophagus. Gastric feeding is adequate in patients who are fed in an upright position or are ambulatory and have a good gag reflex. Although lesser problems, such as diarrhea, bloating, and cramping may occur during gastric feeding, these patients must have a good gag reflex. In comatose or stuporous patients, patients with no gag reflex and patients who are usually in a horizontal position, duodenal placement is necessary. A feeding pump should be used for duodenal feedings to minimize the wide fluxes in feeding rates that occur with gravity-drip devices. Such sudden increases can cause

dumping-like symptoms. Jejunal placement reduces the risk of tube-feeding aspiration. A feeding pump is mandatory. Since the stomach and duodenum have been bypassed, a number of digestive and regulatory functions are not working; therefore, an elemental formula is necessary.

FORMULAS

Choosing the appropriate formula requires knowledge of the caloric, water, and nitrogen requirements of the patient and consideration of dietary restrictions due to organ failure. Also required is a knowledge of the many feeding formulas available. Five groups of formulas can be distinguished: (1) natural blenderized foods; (2) oral nutritional supplements; (3) polymeric lactose-free formulas; (4) monomer lactose-free formulas; and (5) special formulas.

1. Natural blenderized foods. These are recommended for tube feeding patients with head and neck disease or mechanical limitations which preclude solid food consumption but with a normal GI tract:

Compleat B Modified® and Vitaneed® are lactose-free for patients who may be lactose-intolerant.

Compleat B Modified®	Compleat B®
Vitaneed®	Formula 2®

2. Oral nutritional supplements. These products are highly palatable and the least costly to purchase. They are used to supplement an inadequate intake of solids. All of these products contain lactose.

Sustagen® + Water	Carnation™ Instant Breakfast
*Meritene® Liquid	Meritene® + Milk

3. Polymeric lactose-free formulas. Because these formulas contain undigested proteins and long-chain carbohydrates, digestion of these substances must be intact. Precision® LR and Precision® HN have essentially no fat, whereas Travasorb™ MCT and Osmolite® have medium-chain triglycerides as the major fat source. All of these formulas

contain 1 cal/cc, except for Ensure® Plus and Sustacal® HC, which have 1.5 cal/cc, and Magnacal®, Travasorb™ MCT, and Isocal® HNC, which have 2.0 cal/cc. The following formulas are generally palatable and may be taken by mouth or by tube:

*Ensure®	*Ensure® Plus	Travasorb™ Liquid
*Isocal®	Precision® LR	Sustacal® HC
*Magnacal®	Osmolite®	Renu®

4. Monomeric lactose-free formulas. Designed for patients with compromised digestion, these formulas contain hydrolyzed proteins and/or crystalline amino acids. All contain 1 cal/cc. Criticare™, Vivonex®, and Vivonex® HN are low in fat, whereas Vital™, Travasorb™ Standard, and Travasorb™ HN have at least 10% of calories as fat. Travasorb™ HN, Travasorb™ Standard, and Vipep® use MCT oil as the major fat source.

*Vivonex®	Vipep®	Criticare™ HN
*Vivonex® HN	Vital™	Travasorb™ Standard

5. Special formulas. These formulas are suspendable powders of amino acids, carbohydrates, and fat. Adequate mineral and vitamin supplements must be added.

*Amin-Aid®: Designed for use in renal insufficiency, this formula has the essential amino acids plus Histidine with low Na^+ and K^+ content.

*Hepatic-Aid®: A high ratio of branch-chain amino acids to aromatic amino acids in addition to negligible electrolytes make this formula useful for treating hepatic encephalopathy.

Monomeric formulas are elemental diets of digested proteins or synthetic amino acids. No vitamin K is present. While polymeric formulas cost the least, they must be digested by pancreatic and brush border enzymes. They cannot be used for jejunal tube feedings.

Protein content ranges from 8-26%, depending on the type of formula. Similarly, fat content ranges from 1-47%, mostly long-chain triglycerides from corn, soy, or safflower oil. Coconut oil can be added to supply medium-chain triglycerides.

None of these formulas supplies any of the essential fatty acids, and these, principally linoleic acid, must be added. Special formulas are available. Patients with renal or hepatic failure may require decreased protein intake. Carbohydrates must be decreased in patients with pulmonary failure so as to lesson the carbon dioxide load. Patients with steatorrhea should have carbohydrate substituted for a portion of their fat intake.

BEGINNING THE FEEDINGS

Several methods of beginning tube feedings are used. Two examples are provided (Table 1 and 2). If any level of feeding is not tolerated, drop back one step and resume the schedule at that point.

The patient must be monitored closely, especially during initial feedings. Gastric residual should be checked every 2 hours initially, and later every 4 hours. The aspirate is then reinstilled. If the amount exceeds 50 cc plus the amount infused in the last hour, the rate must be dropped back one step.

Gravity drip rates should be monitored every 30 minutes, and pump rates should be checked every hour. Vital signs are monitored every 4 hours. Urinalysis for sugar and acetone should be done every 4 hours initially and once during each nursing shift. Blood tests required vary among physicians, but generally, daily electrolytes, blood urea nitrogen, and glucose are closely monitored, followed by weekly SMAC-20 and complete blood count. Nutritional assessments should be repeated every 10-14 days.

COMPLICATIONS

Too rapid refeeding in a chronically starved patient can be fatal. Metabolic processes in severe malnutrition are reduced to a minimum, prolonging the duration of semi-starvation. In the process, the metabolic burden on failing organs is reduced. On refeeding, this quiescent state is

rapidly reversed with marked increase in insulin and thyroid activity and the adrenergic endocrine systems, although blood pressure remains low. Disease in any one organ system may alter this response, so that special formulas may be needed to avoid hepatic, renal, or cardiac failure.

The most dangerous complications are metabolic, particularly, fluid and electrolyte. Dehydration may be caused by diarrhea, excessive protein intake with obligatory renal water loss, and by an osmotic diuresis, usually from hyperglycemia and glucosuria. A "tube-feeding syndrome" of dehydration, azotemia, hypernatremia, hyperchloremia, and decreased level of consciousness has been identified, caused either by inadequate fluid intake or excessive protein intake. Urine specific gravity can suggest dehydration if renal function is normal and specific gravity is greater than 1.030. /8/ Urine sugars obtained during each nursing shift will detect significant hyperglycemia. Other abnormalities to watch for are hyperkalemia, hypokalemia, and hypophosphatemia.

Diarrhea, the most common complication, is often caused by an excessively hyperosmolar solution in the gut lumen, resulting in a dumping-like syndrome. With too rapid advancement of the feeding rate, water is drawn from the venous capillaries by diffusion to equalize osmolarity of the nutrient solution, leading to bloating, hypermotility, and diarrhea. Therapy consists of decreasing the feeding rate or concentration to the previously tolerated level, and then more gradual advancement. If the feeding tube slips from the stomach into the duodenum, there is less dilution of the feeding formula with gastric secretion, resulting in a hyperosmolar solution. An accidental increase in the feeding rate, or use of bolus feedings, can easily cause the same problem. Bolus feedings should be avoided.

A low-serum albumin may provide insufficient absorbing power of the villous capillaries. Nutrients not absorbed hold water in the bowel lumen, causing diarrhea. Intravenous albumin may be given during dilute tube feedings to control the diarrhea until endogenous albumin production increases. A myriad of drugs may cause diarrhea: antacids, antibiotics, and cardiac medications. Lomotil™ or Immodium™ may help until the offending agent can be removed. Most adults are lactose-intolerated, and lactose-containing feedings may cause diarrhea.

Gastric retention may develop with too rapid advance of a hyperosmolar calorie-rich formula. Stomach contents must be diluted with gastric secretions until an iso-osmolar fluid is produced which can be passed into the duodenum. Until iso-osmolarity is reached, the stomach retains its contents. Correct treatment is reduction of the rate or dilution of the formula.

Diarrhea or gastric retention develops in 10-20% of tube-fed patients. This can usually be controlled by reducing the rate of administration or the strength of the formula.

Elemental diets contain no vitamin K; therefore, special care must be taken in patients on antibiotics to avoid a coagulopathy.

COST

The cost of enteral nutrition formulas varies widely (range, $1 to $9 per 1000 kcal), but is far below that of parenteral nutrition ($25 to $30 per 1000 kcal).

TABLE 1

FIRST METHOD OF BEGINNING TUBE FEEDING

Strength	Rate	Time
Full	25 ml/hr	8 hr
Full	50 ml/hr	8 hr
Full	75 ml/hr	8 hr
Full	100 ml/hr	8 hr
Full	125 ml/hr	

TABLE 2

SECOND METHOD OF BEGINNING TUBE FEEDING

Strength	Rate	Time
One-half	50 ml/hr	8 hr
One-half	75 ml/hr	8 hr
One-half	100 ml/hr	8 hr
Three-fourths	100 ml/hr	24 hr
Full	100 ml/hr	24 hr
Full	125 ml/hr	

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WRITING TOTAL PARENTERAL NUTRITION ORDERS

CPT Jill Lindberg, MD, MC

After completing nutritional assessment and determining the nutritional requirements, total parenteral nutrition (TPN) orders are written, using available guidelines (Appendixes I-III). A nutritional assessment should be done frequently and systematically after the initial examination to assess the progress of TPN patients.

Most TPN patients at this hospital receive the standard LIVN solution. We use DA Form 4700 (Appendix I) to assist in writing these orders. Orders for vitamin K are written separately on DA Form 4256 (Appendix II) as a medication order. Insulin may be added to LIVN solutions as required. Subcutaneous insulin orders should be written as a sliding scale dosage on the regular physicians' form.

LIVN orders should be written by 1300 hours daily. A change in orders requires at least 4 hours' notice for the pharmacist to fill the order. Do not make trivial (5-10 mEq) changes in electrolytes on an emergency basis and expect to balance your patient's serum electrolytes through the LIVN solution. Rather, balance electrolytes with a peripheral IV line and gradually incorporate these changes into the LIVN solution, just as you would for sliding scale subcutaneous insulin. Remember, a critically ill patient is likely to be very sensitive to small changes in electrolytes and TPN may be hazardous. Do not expect to manage a metabolically unstable patient effectively through frequent, last-minute changes in LIVN electrolyte concentrations.

We generally start LIVN at 40 cc/hr and increase the rate as outlined in Appendix III. It is also recommended that a test dose of Liposyn® be given initially as 1 ml/min infused over a 30-minute period to rule out adverse reactions. Administration of lipid solutions should not exceed 1.05 mg/kg/hr. We generally recommend that 500 ml of a 10% solution be given over an 8-hour period.

Follow the standard non-medication form for ordering laboratory test (Appendix II) to monitor patients receiving TPN. Never terminate a TPN infusion abruptly. Always taper the rate of infusion or substitute a bottle of 10% glucose to avoid hypoglycemia. Consult the surgical service for adjustment of TPN solution rates in patients requiring surgery several days before surgery is anticipated.

APPENDIX I

MEDICAL RECORD – SUPPLEMENTAL MEDICAL DATA

For use of this form, see AR 40-400; the proponent agency is the Office of The Surgeon General.

REPORT TITLE: Total Parenteral Nutrition (TPN) Standing Orders

OTSG APPROVED (Date)

TPN information –
call Ext. 4376 - Pharmacist Consult
Ext. 2073 - Physician Consult

TPN administration times are:
(1) 1500 & 0300 = 40-80ml/hr
(2) 1100, 1900 & 0300 = 100-125ml/hr

Diagnosis:

NURSING UNIT	ROOM NO.	BED NO.

STANDARD TPN	CHECK		
Nitrogen (1GM N_2 = 6.25Gms Protein)		4Gm	
Dextrose		30%	
Na+		40mEq	
K+		40mEq	
Phosphorus (Elemental)		419mg	
Cl^-		60mEq	
Ac^-		40mEq	
Mg++		8mEq	
Ca++		5mEq	
Zn++		2mg	
Cu++		0.4mg	
MVI-12		10ml/day	
Water for inj to make		1000ml	
Non-protein calories		1020 Kcal	

STANDARD PROTOCOL RATE: 40ml/hr first 24 hrs; then as determined by physician.

NONSTANDARD TPN	CHECK	
Nitrogen (as Amino Acid 10%)		Gm
Nitrogen (essential Amino Ac)		Gm
Dextrose		%
Na+		mEq
K+		mEq
Phosphorus (Elemental)		mg
Cl^-		mEq
Ac^-		mEq
Mg++		mEq
Ca++		mEq
Zn++		mg
Cu++		mg
MVI-12		ml
MVI Conc (5N use only)		mg
L-Cysteine		mg
Fe++		mg
Insulin, Reg		Units
Other		
Water for inj to make		1000ml

Vit. K 10mg IM weekly
Rate changes
} Write orders on DA Form 4256

New TPN orders to IV pharmacy NLT 1300.
Changes require 4 hours notice; otherwise, will be effective with next TPN bottle.

Obligated cations/anions
Ac^- - 10mEq/Gm Nitrogen (Aminosyn 10%)
13mEq/Gm Nitrogen (Aminosyn RF)
K^+ - 4.4mEq/93mg Phosphorus
Na^+ - 4mEq/93mg Phosphorus
Ac^- - Adjusted to balance by pharmacist
RATE: _____ ml per hour

Non-protein calories:
Dextrose = 3.4 Kcal/Gm
10% Fat Emulsion = 1.1 Kcal/ml
20% Fat Emulsion = 2.0 Kcal/ml

Fat Emulsion 10% ( )
Fat Emulsion 20% ( )
Adm rate: ml/hr _____
on M T W Th F Sa Sun or daily (circle)

Phone No. _____ Beeper No. _____ Time _____

PREPARED BY (Signature & Title)	DEPARTMENT/SERVICE/CLINIC	DATE

PATIENT'S IDENTIFICATION (For typed or written entries give: Name - last, first, middle; grade; date; hospital or medical facility)

☐ HISTORY/PHYSICAL ☐ FLOW CHART
☐ OTHER EXAMINATION OR EVALUATION ☐ OTHER (Specify)
☐ DIAGNOSTIC STUDIES
☐ TREATMENT

DA FORM 1 MAY 78 4700

Nutritional Support Symposium for the Internist, Summer 1983

CLINICAL RECORD - DOCTOR'S ORDERS

For use of this form, see AR 40-400; the proponent agency is the Office of The Surgeon General.

THE DOCTOR SHALL RECORD DATE, TIME AND SIGN EACH SET OF ORDERS. IF PROBLEM ORIENTED MEDICAL RECORD SYSTEM IS USED, WRITE PROBLEM NUMBER IN COLUMN INDICATED BY ARROW BELOW.

PATIENT IDENTIFICATION

NURSING UNIT | ROOM NO. | BED NO.

DATE OF ORDER TIME OF ORDER

STANDARD LIVN ORDERS (MEDICATION) HOURS

1) Begin LIVN @ cc/hr @ hours

2) Sliding Scale Regular Insulin
Glucose 250-300mg%—5u. Reg Insulin IV
Glucose 301-350mg%-10u. Reg Insulin IV
Glucose 351-400mg%-15u. Reg Insulin IV
Glucose over 400mg% - Notify H.O.

3) Vitamin K 10mg IM q Monday

LIST TIME ORDER NOTED AND SIGN

PATIENT IDENTIFICATION

NURSING UNIT | ROOM NO. | BED NO.

DATE OF ORDER TIME OF ORDER

_____ HOURS

STANDARD LIVN ORDERS (NON-MEDICATION)

1) Strict I&O daily

2) Daily body weight

3) LABS:

a) Initial SMAC-20 q day X 3 (Lytes, BUN & Glucose - weekends/holidays)

b) SMAC-20 q M-W-F thereafter.

PATIENT IDENTIFICATION

NURSING UNIT | ROOM NO. | BED NO.

DATE OF ORDER TIME OF ORDER

_____ HOURS

c) CBC with Diff, PT, PTT, Cu, Fe, TIBC, Mg++, Zn initially after catheter insertion then, q Monday.

4) Urine sugar every voiding or q 4hrs if catheterized (use testape/Ketostix)

5) Urine specific gravity q voiding or q 4hrs if catheterized.

PATIENT IDENTIFICATION

NURSING UNIT | ROOM NO. | BED NO.

DATE OF ORDER TIME OF ORDER

_____ HOURS

6) "URGENT" Blood Glucose & K+ for urine sugar 2+ or greater - Notify H.O.

7) Serum Osmolality for glucose over 400mg%

8) Repeat blood glucose & K+ 1 hr after insulin dosage - Notify H.O.

DA FORM 1 APR 79 4256 REPLACES EDITION OF 1 JUL 77, WHICH MAY BE USED.

MANAGEMENT OF PATIENTS ON LIVN SOLUTION

1. Begin infusion slowly. Infuse 40 cc/hr on the first day, 90 cc/hr on the second day, and 120 cc/hr on the third day. The LIVN solution should run continuously. The remainder of the patient's daily fluid requirements should be given via the peripheral venous route. If significant glycosuria occurs during initiation of LIVN therapy, do not advance the infusion rate. The rate should be increased slowly when glycosuria abates. If holding the infusion rate fails to relieve glycosuria, add regular insulin to the LIVN solution. A starting dose of 10-20 units of regular insulin may be added per liter of standard LIVN solution. Careful monitoring of blood glucose is critical during this period of therapy. The blood glucose should be maintained below 200 mgm%, and the urine sugar should be negative, as well.

2. If possible, adult patients should receive approxiately 12-124 gm of linoleic acid daily. In patients able to take oral nutrition, this may be supplied by 1 oz of corn oil (or 20 cc of safflower oil) given daily in divided doses. In adult patients where oral intake is not possible, give 500 cc Intralipid® at least twice weekly to avoid essential fatty acid deficiency.

3. Discontinuation: LIVN solution should be slowly tapered over 2-3 days. Infuse at 80 cc/hr on the first day, 40 cc/hr on the second day, and discontinue on the third day. Careful monitoring of blood glucose is required. Monitoring oral intake is important during this transition. Monitoring should continue until adequate intake is achieved.

MANAGEMENT OF PATIENTS ON INTRAVENOUS FAT EMULSIONS

Obtain a baseline serum triglyceride determination. Samples for serum triglycerides should be drawn prior to each increase in dosage. Intralipid® should be started at 0.5 gm/kg/day and increased in increments of 1.0 gm/kg/day every 24 hours. The maximum allowable dose is 2.5 gm/kg/day in adults and 4 gm/kg/day in children. Intralipid® should be infused at a rate no greater than 1.05 gm/kg/hour.

Coagulopathies are associated with fat emulsions; platelet counts, PT and PTT should be determined before and 24 hours after the first infusion, and weekly thereafter. Fat emulsions ideally should be administered alone, via a peripheral intravenous route.

CARE OF THE CENTRAL VENOUS CATHETER

Central venous catheter insertion requires the following skin preparation:

1. Acetone/alcohol scrub
2. Betadine™ scrub
3. Isopropyl alcohol 70%
4. Betadine™ solution

The catheter should be sutured to the chest wall in a manner that does not interfere with shoulder joint motion. Give only LIVN solutions through the catheter. Additions to LIVN containers should be done only under a laminar flow hood, by a pharmacist. Do not draw or infuse blood through the LIVN catheter. The entire infusion apparatus should be replaced every 12 hours.

The Nutrition Support Services should change the catheter dressing on all patients. Parenteral nutrition catheters require meticulous care. For complete details on catheter dressing care, see the LAMC Nursing Procedure, available on all nursing units.

FEVER PROTOCOL

Patients receiving parenteral nutrition who develop sepsis from central venous catheters may show persistent temperature spikes to 38.9 °C to 40.0 °C every 12-24 hours. Evaluating the central venous catheter as the etiology for febrile episodes is often difficult because many patients have other potential sources of fever. The following procedures have been useful in documenting central venous catheter-induced sepsis:

Asceptically discontinue the bottle of LIVN solution, hang 10% dextrose in water in its place and send the LIVN bottle immediately to the pharmacy to be cultured. Notify the Nutrition Support Service.

Look for other potential sources of infection. For example, repeat the history and physical examination, then obtain peripheral blood cultures, urine cultures, throat and sputum cultures, wound cultures, and stool cultures, as indicated clinically.

If a source of infection other than the catheter is determined or suspected by clinical judgment, treat that source with appropriate antibiotics. If no other source of infection is found and the patient does not respond to empiric use of antibiotics, notify the Nutrition Support Service. A joint evaluation with the Infectious Disease Service is in order, and the catheter will have to be replaced. For removal of the catheter, notify the Nutrition Support Service. The catheter tip will be sent for culturing.

METABOLIC COMPLICATIONS OF LIVN AND THEIR TREATMENT

1. Hyperosmolar nonketotic dehydration

   a. Characterized by:

      Hyperglycemia
      Increased serum osmolality
      Dehydration
      Headache
      Confusion
      Somnolence, coma
      Seizures
      Metabolic acidosis (pH usually between 7.4 and 7.2)

   b. To determine cause:

      Check for inadvertent increased rate of LIVN administration such as a change in the pump setting, error in drip chamber, or effort to "catch up" IV rate.

Check for hypokalemia
Check for sepsis and stress
Check insulin requirements

c. To treat:

Give regular insulin IV to correct hyperglycemia.
Give free water as 5% dextrose in half-normal saline at about 250 cc/hr.
Replace half of estimated deficit in first 12 hours, remainder over 24-36 hours.
Monitor serum glucose, sodium, potassium, serum osmolarity, and serum pH.
Intravenous bicarbonate may be needed, particularly if the serum pH is 7.2 or less.

2. Hypoglycemia

a. Characterized by:

A tingling sensation of mouth and extremities
Rapid pulse
Cold, clammy skin
Thirst
Lethargy, somnolence, coma
Seizures

b. Caused by:

Interruption or rapid decrease in LIVN administration
Excessive insulin infusion

c. To treat:

Give 50% dextrose in water "IV push."
Start a 10% dextrose infusion at 50 cc/hr.
Obtain serial blood glucose and potassium determinations.
Correct line malfunctions
Adjust insulin dosage

3. Hypophosphatemia

a. Characterized by:

Weakness
Tremors and ballismic movements of upper extremities
Mental confusion progressing to coma
Hemolytic anemia

b. Caused by:

Respiratory alkalosis
Gram negative bacteremia
Salicylatye intoxication
Excess antacid ingestion
Hyperparathyroidism
Vitamin D deficiency
Fanconi syndrome
Hypokalemia, hypomagnesemia
Chronic alcohol abuse
Congenital renal tubule disorders

c. To treat:

Add phosphate to LIVN solution,
Closely monitor potassium, magnesium, calcium, glucose, and phosphorous.

4. Hyperchloremic acidosis

a. Characterized by:

Decrease in arterial blood pH
Decrease in plasma bicarbonate
Increase in plasma chloride

b. Caused by:

Improper acetate/chloride ratio in LIVN (chloride ion should equal Na ion)
Excessive renal or gastrointestional loss of base

c. To treat:

Substitute acetate for chloride (requires normal hepatic function)

5. Hyperammonemia

   a. Characterized by:

      Elevated serum ammonia levels
      Lethargy, somnolence, coma
      Seizures

   b. Caused by:

      Arginine deficiency in TPN solutions
      Hepatic dysfunction
      High nitrogen load

   c. To treat:

      Decrease nitrogen needs.
      Increase arginine content of LIVN solution.
      Evaluate for liver dysfunction.

6. Hypokalemia and hyponatremia

   a. Characterized by:

      Abnormal reflexes
      Abnormal EKG
      Mental changes

   b. Caused by:

      Excessive gastrointestinal or urinary losses
      Deficiency in LIVN solutions
      Medications

   c. To treat:

      Replace ions and re-evaluate fluid and electrolyte losses.
      Restrict fluid intake if necessary.
      Adjust medication dosages.

7. Hypomagnesemia

   a. Characterized by:

Arrythymias, hallucinations, ileus, hyperreflexia, vertigo
Weakness
Seizures and tetany

b. Caused by:

Insufficient magnesium intake

c. To treat:

Give 2-4 ml of 50% magnesium sulfate IM every 6 hours in an emergency situation.
Give supplemental doses of 64-128 mEq magnesium every 24 hours for 2-3 days.
Obtain serum magnesium levels weekly.

Some other potential metabolic complications of TPN include hypocalcemia, hypercalcemia, and hypermagnesemia.

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GPO 691-169 / 306


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